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THE EFFECT OF VENTRICULAR ASYSTOLE ON RESPIRATION[1]

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Submitted for publication June 27, 1936

Syncope associated with slowing of the heart rate was first described by Adams (1) in 1827. He commented on the respiration during the syncopal attacks by saying that the breathing became "loudly stertorous." Stokes (2), whose name is linked with that of Adams in the syndrome of syncopal attacks produced by sudden heart-block, published his observations in 1846 and his attention, like that of most subsequent authors, was focussed on the circulatory phenomena to the exclusion of the breathing. Sir Thomas Lewis (3) (1925) writes "The blood is dammed back in the venous system, increasing pallor has cyanosis added to it, the breathing deepens and becomes stertorous; twitching of the face and upper limbs eventuates." Recent physiological experiments have shown that breathing is affected by changes in blood flow to the brain (7, 8) and that it is also influenced by changes in blood pressure in the carotid arteries (9, 10, 11). Unfortunately, the complex experiments which demonstrate these facts in laboratory animals cannot be reproduced in human beings.

We have had recently on the medical wards a patient who suffered from heart-block with attacks of asystole lasting, some of them, as long as 70 seconds and recurring at such short intervals that we were able to obtain tracings of the respiration during a number of them.

The patient was a 61-year-old white woman who was admitted on February 2, 1936, to the Medical Service of the Johns Hopkins Hospital (Unit No. 67811) suffering from fainting attacks of 3 years' duration. Except for some dyspnoea on exertion her history was unenlightening. There was nothing to suggest that

[1] Presented in brief before the Association of American Physicians, May 6, 1936.

she had suffered from rheumatic fever or syphilis. The fainting attacks, which had begun about three years previously, had recurred at first at long intervals of three or four months but during the past year had become more frequent. She would feel faint, would lose consciousness for a few seconds and on awakening often would be nauseated and would vomit. There was never any pain in the chest. Four months before admission she was seen in the Out-Patient Department and found to have first degree heart-block and bundle-branch block of the common variety and at this time her blood pressure was 110/90. The attacks came in groups but some improvement was noted from the use of luminal. She was entirely free of syncopal attacks during the last two weeks of January but she had ten on the day of admission before reaching the hospital.

On examination she was seen to be an obese, elderly white woman, height 5 feet, 2 inches; weight 203 pounds. Temperature 98.6°, respirations 20, pulse 32 with periods when it would be imperceptible for 5 to 20 seconds. The respiration was Cheyne-Stokes in character and there were frequent syncopal attacks. The heart was slightly enlarged, there was an apical systolic murmur; the ventricular sounds were slow and regular and to the left of the sternum much more rapid auricular sounds were heard. There was evidence of mild congestive failure in the form of râles at the lung bases and slight oedema of the ankles. The liver dullness was not enlarged.

Urine: Specific gravity 1022, albumin trace, sugar 0, acetone present (strongly positive test), diacetic acid 0. Microscopic: Occasional cast.

Red blood corpuscles 5.95 million, haemoglobin 116 per cent. White blood cells 20,240 with a normal differential count; Wassermann negative. Total protein 7.5 grammes per cent; CO_2-combining power 51 volumes per cent.

On the ward it was observed that frequent periods of asystole occurred, during which the pulse stopped and the apical heart sounds disappeared. At these times her respirations became rapid and slightly noisy, she grew increasingly pale and after about 15 seconds usually lapsed into unconsciousness, although in one attack it was observed that she remained conscious for 40 seconds of asystole. After 30 to 50 seconds she became restless and made convulsive movements of the head and arms, and the eyes rolled up and toward one side or the other with slight nystagmoid jerks. With the first beat terminating the asystole her face flushed suddenly, she took one or two breaths, promptly regained consciousness and lapsed into apnoea or very slow and shallow breathing with a regular pulse rate of about 30 beats to the minute. Her face gradually lost its flush and her breathing increased and these attacks were occasionally followed by vomiting. An electrocardiogram made on the day of admission revealed that complete auriculo-ventricular dissociation existed with periods of ventricular stand-still lasting from 5 to 20 seconds. Later extensive records (Fig. I) showed that the auricular and ventricular complexes varied, particularly just before and just after the periods of asystole, and occasionally following asystole there were periods of ventricular tachycardia with a rate of 100. With the advent of complete heart-block the bundle-branch block of the common variety had been replaced by bundle-branch

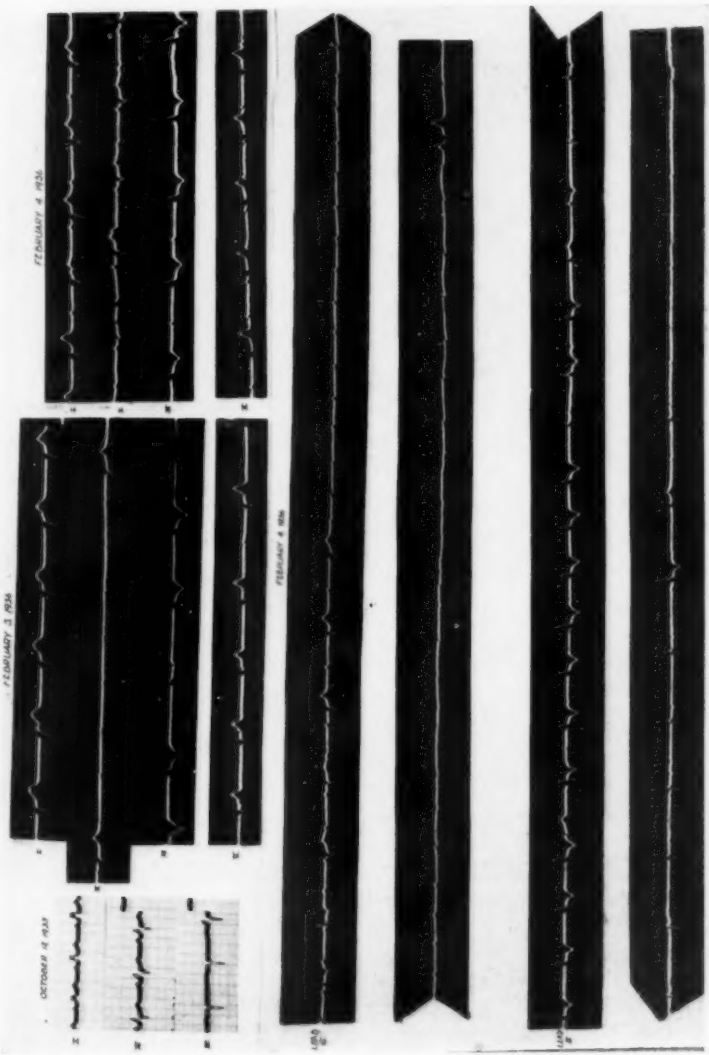

FIG. I. CHARACTERISTIC STRIPS FROM ELECTROCARDIOGRAPHIC TRACINGS SHOWING LONG PERIODS OF ASYSTOLE AS WELL AS VARIATIONS IN THE VENTRICULAR COMPLEXES

block of the uncommon variety, indicating activity of an ectopic focus on the side of the previously blocked bundle branch. Just before periods of asystole the amplitude of the ventricular complexes became smaller and finally, just before dropping out, the main deflection changed to the opposite sign. The first few ventricular beats after asystole arose from various ectopic foci and then the usual form was resumed.

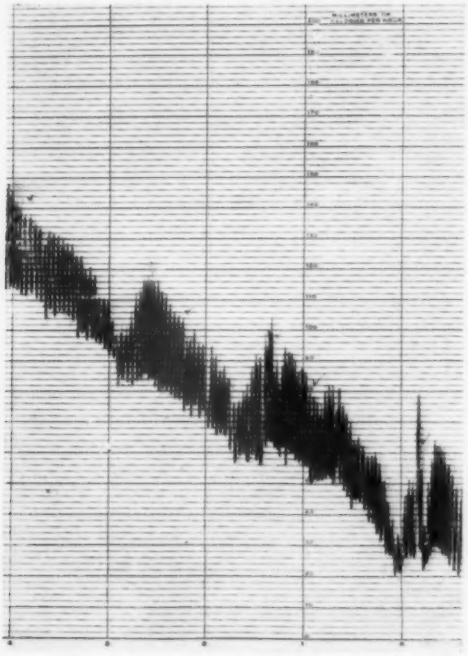

FIG. II. TRACING OF RESPIRATION
Arrows denote beginning and ending of 3 short periods of asystole

These periods of asystole followed each other every minute or two during the entire period that she lived after admission, which was 4 days. They gradually grew longer. Treatment had little or no effect. During the course of the first 12 hours in the hospital she received 10 ampoules of digifolin and 0.2 gramme of powdered digitalis on the second day and 0.1 gramme a day on the next three days. Atropin was administered frequently (1 mgm. hypodermically), adrenalin and ephedrine were given, but all with no noticeable effect on the periods of asys-

tole. The administration of oxygen in an oxygen tent did not seem to lessen or increase the number or severity of the attacks. After gradually growing weaker she died on February 7th, 1936, at 1.15 a.m. The autopsy findings were essentially negative so far as the general body and vascular system were concerned. There was little if any arteriosclerosis. The valves of the heart were normal.

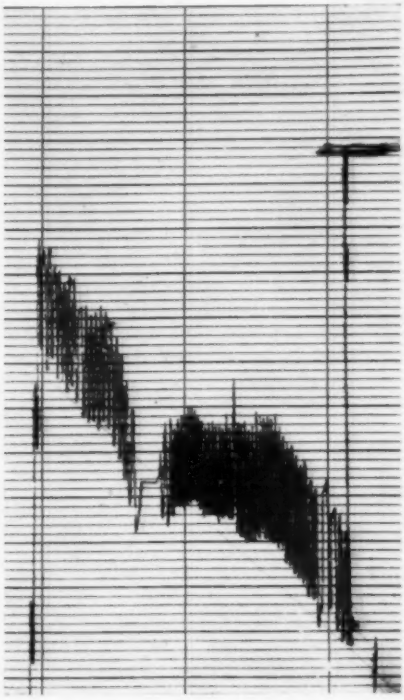

FIG. III. TRACING OF RESPIRATION DURING PERIOD OF ASYSTOLE LASTING MORE THAN A MINUTE
Apparatus filled with oxygen

The heart muscle looked normal to the naked eye except for a large fibrotic area involving the region of the upper portion of the bundle of His. Microscopic examination of the heart muscle revealed a slight amount of scarring. Sections of the fibrous lesion in the bundle of His added no further information as to its origin. There was a shallow ulcer at the lower end of the oesophagus which was thought to have been a result of the frequent vomiting.

In order to study respiration during the periods of ventricular stand-still the patient was allowed to breathe into a spirometer. Figure II shows a tracing of the respiration made February 4th with a Benedict-Roth metabolism apparatus during periods of asystole which recurred nearly every minute and lasted 20 to 30 seconds. During this time the recording machine was filled with oxygen and

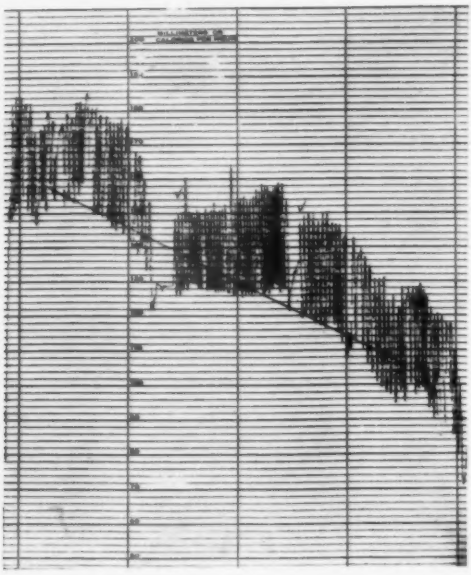

FIG. IV. TRACING OF RESPIRATION DURING PERIOD OF ASYSTOLE LASTING MORE THAN A MINUTE

Apparatus filled with air

the exhaled carbon dioxide was removed by passage through soda lime. It will be seen that the curve suggests rather mild Cheyne-Stokes breathing. During the period of asystole the respiratory rate is only slightly increased but the depth of each breath is augmented. With the resumption of heart beats breathing is depressed, becomes slow and shallow and then gradually builds up again to normal.

Figure III is a tracing recorded on February 6th at which time an

unsuccessful attempt was made to obtain simultaneous pulse tracings. By the time these records were made, the patient had become weaker and the periods of asystole longer, and with this change the alterations in breathing were more pronounced. The recording machine was filled with room air and the carbon dioxide exhaled was removed by passage through soda lime. Figure IV is like Figure III except that the recording apparatus was filled with oxygen.

These tracings (Figs. III and IV) show an abrupt increase in rate of respiration from 23 to 35 to the minute and a levelling off of the curve indicating cessation of withdrawal of oxygen from the machine during asystole. The temporary interference with the bodily oxygen supply, caused by asystole and the resultant cessation of blood flow, is soon compensated for after the ventricles start beating again, as shown by the prompt return to the expected curve of oxygen withdrawal from the apparatus. During asystole the breathing is rapid and of the same depth as before but the depth diminishes toward the end of these periods. Soon after the ventricles commence to beat again, there is sudden and complete apnoea lasting about 15 seconds, after which the usual breathing is rapidly resumed.

These observations provide some information as to the control of respiration during asystole. Since, as far as I can discover, this condition has not been simulated in laboratory animals, it is worthy of careful analysis. It seems quite evident that the intensity of the humoral stimulus to the respiratory centers is changed when the blood flow is interfered with by asystole. Exactly what happens to blood flow following cessation of ventricular beating is problematical. One might expect the arterial pressure to fall promptly to some very low point and from there to fall or rise very gradually depending on the elastic recoil of the large arteries and on the degree of peripheral vasomotor tone that is maintained. Vasomotor tone persists until after death and it seems to be unsettled when and how the major portion of blood reaches the venous side. The usual method of recording systolic and diastolic blood pressure can not be made use of while the ventricles are not beating. Even if accurate information were available about blood flow in the extremities during asystole, this would not elucidate the mechanism of blood flow to the medulla under similar circumstances. For a period of one or two minutes of

cardiac stand-still a very slow forward movement of the blood stream might persist and in this case the medullary centers would be slowly supplied with fresh blood containing ample available oxygen and having a normally low CO_2 content. However this may be, after the arterial pressure has fallen in the first few seconds to its more permanent level, blood flow is quickly reduced to a minimum.

With this sudden reduction in blood pressure and blood flow three conditions develop, each of which is known to influence respiration: (1) The respiratory center (as well as the carotid body) receives a limited supply of oxygen; (2) the respiratory center is suddenly deprived of the usual blood flow; (3) the carotid sinus is affected by a sudden fall in blood pressure (endosinusal pressure). The sensitive end-organ situated at the bifurcation of the common carotid arteries, which has received much attention lately from physiologists, consists of two portions: (a) the *carotid sinus* which is stimulated by raising or lowering the pressure in the artery, thus affecting sensory nerve endings which are situated in the wall of the carotid artery in this region (the stretch receptors); and (b) the *carotid body* which lies outside of the carotid artery in the bifurcation and is supplied with blood through the occipital artery and receives its stimulation in a fashion similar to the medullary respiratory center by changes in the arterial oxygen and CO_2 tension or hydrogen-ion concentration. Afferent impulses ascend through a nerve (nerve of Hering), which arises in these two portions and which joins the glosso-pharyngeal nerve to enter the medulla. Three distinct reflexes result from stimulating the carotid sinus—cardiac, vasomotor and respiratory. The first two forms do not concern us in the present discussion. The carotid body acts in a manner similar to the respiratory center and for our purposes may be grouped with it and, although it is thought to be less sensitive to changes in CO_2 tension or pH of arterial blood than is the respiratory center, its response to anoxaemia is similar.

The three conditions which develop with asystole can be considered in turn:

(1) The respiratory center (as well as the carotid body) receives a limited supply of oxygen. It is evident that the blood which is in the aorta and large arteries when the ventricles cease beating contains oxygen and CO_2 under approximately normal tension and that

this tension changes little, if any, while the blood is in the arteries. The question which arises therefore is whether normal arterial blood passing the respiratory center at a greatly reduced rate of flow produces an anoxaemic effect on the center or not. Haldane (4) has shown that oxygen want does not stimulate respiration until it becomes extreme and actually causes cyanosis. Selladurai and Wright (5) have confirmed this fact by animal experiments in which they showed that oxygen want stimulates respiration only reflexly and that when the vagi are cut and the carotid sinuses denervated the respiratory center is depressed by insufficient oxygen. In our patient the abrupt increase in respiratory rate and the constant slightly diminished depth of breathing are quite different from the breathing observed during increasing anoxaemia. Bogue and Stella (6) studied the afferent impulses in the nerve from the carotid body after circulation in the dog had been interfered with suddenly by cutting across the heart. Blood flow would then be very similar to that in our patient during asystole. By this experiment they recorded the stimulation produced in the carotid body by the chemical changes in the blood which developed after interference with the blood flow and they took the added precaution of denervating the carotid sinus from its stretch receptors. They noted that it took between one half and one minute before the discharge of nerve impulses became as great as that produced by acute anoxaemia in the living animal. We are led to conclude, therefore, that in our patient anoxaemia was not present in the first half minute or more of asystole and, further, that it would not have caused the changes in breathing shown in Figures III, IV and V even if it had occurred.

(2) The respiratory center is suddenly deprived of the usual blood flow. Gesell (7) and others believe the rate of cerebral blood flow regulates the removal from the respiratory center of its own chemically stimulating cellular metabolites. These metabolites might increase rapidly enough after abrupt cessation of blood flow to stimulate respiration almost immediately. In fact this is seen to occur in Schmidt's (8) experiments of occluding the vertebral and carotid arteries by which he obtained sudden dyspnoea that was not altered by denervation of the carotid sinuses (Schmidt's Fig. 2). Since in our patient blood flow to the brain was tremendously reduced during

asystole and since dyspnoea occurred just as in Schmidt's experiment, this factor of blood flow must be given due consideration in seeking for an explanation of the changes in breathing seen during asystole.

(3) The carotid sinus is affected by a sudden fall in blood pressure (endosinusal pressure). Respiratory reflexes arising in the carotid sinus are produced not only by chemical stimulation of the carotid body but also by pressure changes within the carotid artery acting upon the sinus stretch receptors. This respiratory reflex resulting from alterations in endosinusal pressure is not as widely recognized as the cardiac and vasomotor carotid sinus reflexes and it is perhaps more variable. However, fall in endosinusal carotid pressure in laboratory animals has been shown by Moissejeff, (9) Heymans (10), Schmidt (11) and many others to stimulate respiration and produce tachypnoea and hyperpnoea. From these experiments it appears that the carotid sinus maintains a tonic inhibitory control over respiration. The respiratory reflex response to a lowering of the pressure in the carotid sinus is constant and immediate and identical with that noted in our case during asystole.

For the apnoea which develops soon after the return of ventricular beating the same factors must be considered in seeking an explanation. There is, on the one hand, the sudden rise of pressure in the carotid sinus (Heymans' Fig. 9) and the abrupt return of blood flow through the respiratory center (Schmidt's Fig. 2) and, on the other, delivery to the respiratory center of blood which has been subject to hyperventilation. The blood which was more or less stationary in the pulmonary capillaries during most of the period of asystole, besides being fully oxygenated, must have given off nearly all possible carbon dioxide, and it is obvious that the respiratory center would be maximally depressed by blood of this chemical composition. Respiration appears to start again only when this blood passes by the centers and is followed by blood of unusually low oxygen and high carbon dioxide content. To throw light on this point the machine was filled with oxygen containing 5 per cent carbon dioxide. The carbon dioxide percentage undoubtedly fell as the gas was inspired from the tank and expired through a closed container of soda lime back into the tank. This is shown by the continued, although lessened, rise of the curve (Fig. V). Ultimately the carbon dioxide would have been

largely washed out of the tank mixture but at the time of this tracing the tank had just been filled with the mixture. The fact that maintenance of the carbon dioxide content of the blood, which was delayed

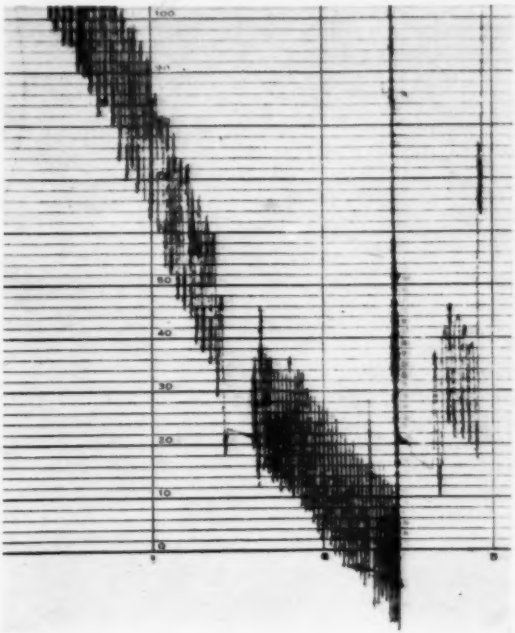

FIG. V. TRACING OF RESPIRATION DURING PERIOD OF ASYSTOLE LASTING MORE THAN A MINUTE

Apparatus filled with oxygen 95 per cent and carbon dioxide 5 per cent

in the pulmonary circuit during asystole, by breathing a CO_2 mixture, did not abolish the period of apnoea tends to eliminate, in this case, as it did in Schmidt's experiment also,[2] abnormally low arterial CO_2 as a cause of the apnoea.

[2] Schmidt, C. F.: Reference 8, page 121: "To show that the apnea was not due to loss of CO_2 from the blood during the hyperpnea resulting from the occlusion, the experiment was repeated during inhalation of 10 per cent CO_2. The apnea produced by release of the vessels was not prevented thereby (Fig. 2)."

Whether we incline to the Gesell hypothesis of blood flow for explanation of both of these occurrences (that is, the abrupt change from normal breathing to rapid, even, breathing and then the sharp cessation of breathing) or to the respiratory reflex initiated by changes in

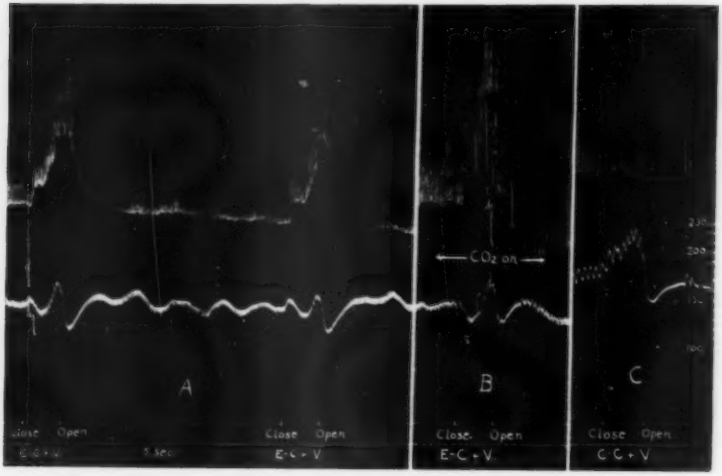

FIG. VI. TRACING REPRINTED FROM AN ARTICLE BY SCHMIDT (11) IN THE AMERICAN JOURNAL OF PHYSIOLOGY, 1932

Fig. 2. Apnoea upon release of occluded carotid and vertebral arteries--dog. Barbital; respiratory plethysmograph in A and B, pneumograph in C; otherwise same as figure 1.

A—vagi and sinuses intact, air breathing.

B—CO_2—O_2 (10 per cent—90 per cent) inhalation throughout—otherwise same as A.

C—vagi cut, sinus regions excised.

the endosinusal carotid pressure, depends largely on future laboratory experiments.

Apnoea has been produced in laboratory animals by Selladurai and Wright (5) by depressing with low oxygen gas mixture the respiratory center after denervating the carotid sinuses and cutting the vagi. With these "buffer nerves" intact, however, such exhaustion of the respiratory center occurred only after six or seven minutes of oxygen

want and therefore I am inclined to deny the possibility of such an explanation for the apnoea in our case.

Although the respiratory changes shown in Figures III, IV and V are clearly secondary to changes in circulation, it seems quite possible that such a condition as is represented in Figure II may be the result of reciprocal action of Cheyne-Stokes breathing and rapidly recurring asystole on each other. That is, asystole produces altered respiration which in turn enhances the factors (such as unevenness of oxygen supply to the myocardium) which initiate asystole.

The phenomenon of flushing of the face may have an important confirmatory value. It too probably depends on a carotid sinus reflex and is produced in a manner similar to that reported by Weiss (12) in patients who develop syncope without change in heart rate or blood pressure from external pressure over the carotid sinus. In these patients pallor was produced by carotid sinus pressure and flushing accompanied release of the external pressure which, it would seem, may have permitted a rise of endosinusal pressure. In our case the sudden rise of pressure in the carotid artery was undoubtedly followed by peripheral vasodilatation. However, another possible explanation of the flushing is to be found in the similar reaction described by Sir Thomas Lewis (13) when the capillaries of an extremity dilate after the removal of a tight tourniquet. This is thought to be due to the loss of tone of the capillaries developed during the anoxaemic period of absent blood flow and caused by metabolites formed during the period of anoxaemia. If this phenomenon is produced by the vasomotor carotid sinus reflex, there is more reason to hold a similar respiratory carotid sinus reflex responsible for the production of the dyspnoea and apnoea which occur in this case.

Pertinent articles on the subject of this paper are few and of recent date. There have been many reports of alteration in cardiac rate and rhythm secondary to Cheyne-Stokes respiration (Cohn and Lewis (14), Resnik and Lathrop (15), Hamberger, Katz and Rubenfeld (16), von Hoesslin (17), Steele and Anthony (18)), and Oppenheimer and Williams (19) describe changes in auricular rate and ventricular complexes in a patient with complete heart-block. Bäumler (20) in 1912 actually described asystole (Herzstillstand) of 30 seconds' duration which he thought due to the effect on the vagus center in the

medulla of blood which had been over-oxygenated during the periods of hyperpnoea of Cheyne-Stokes breathing. Such an explanation, even if tenable in other respects, is not applicable to cases of complete auriculo-ventricular dissociation such as the one recorded in this paper. Griffith (21) in 1921 described a case of dyspnoea and apnoea associated with Adams-Stokes attacks but gave no explanation. Wenckebach and Winterberg (22), in their book "Die unregelmässige Herztätigkeit," cite a case of complete heart-block with periods of asystole associated with dyspnoea preceded by apnoea. They thought the asystole was a result of asphyxia of the heart muscle and of the conduction system caused by the periods of apnoea. The records we have obtained show that the periods of apnoea follow asystole rather than precede it, although when the attacks come close together it might be difficult to make this distinction.

Averbuck (23) in 1932 was the first author to consider the possibility that the respiratory irregularities may be secondary to the periods of ventricular asystole. He reported the case of a 42-year-old man with coronary occlusion and complete heart-block, who suffered from Adams-Stokes attacks caused by periods of ventricular asystole which were associated with dyspnoea and followed by apnoea. He argued that the periods of hyperpnoea and apnoea were caused by the periods of asystole, since they were seen only when the heart stopped beating and they disappeared when the patient regained compensation, although the periods of asystole persisted. Averbuck obtained no records of the respiration and his explanation was mainly concerned with establishing the fact that arrhythmia of the heart was the dominating condition rather than the Cheyne-Stokes respiration.

Hill and MacKinnon (24) reported, in 1934, a case presenting features almost identical with the one here reported in which complete auriculoventricular block was due, they thought, to bilateral bundle-branch lesions, although the branches of the bundle were not included in the microscopic sections of the heart which were studied *post mortem*. From Mackenzie polygraph tracings, in which the respiration was recorded simultaneously with the brachial pulse, they observed a form of Cheyne-Stokes respiration associated with periods of asystole recurring in rapid succession. Longer asystolic periods (70 to 90 seconds) were associated with a frankly asphyxial behavior

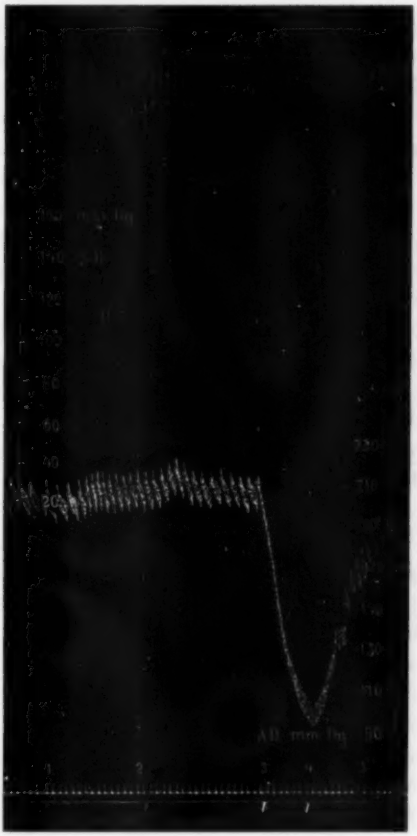

FIG. VII. TRACING REPRINTED FROM AN ARTICLE BY HEYMANS, BOUCHAERT AND DAUTREBANDE (10) IN PFLÜGER'S ARCHIV, 1932, WHICH SHOWS APNOEA PRODUCED BY ELEVATION OF PRESSURE IN THE ISOLATED CAROTID SINUS

A—respiration. S.D.—intrasinusal pressure. A.D.—femoral artery pressure. At 3 intrasinusal pressure is raised from 80 to 160 mm. Hg and apnoea results. At 4 intrasinusal pressure is lowered to 40 mm Hg and tachypnoea results.

of the respiration, the movements becoming deepened and faster, then slower and still deeper and finally ceasing after a variable number of gasping convulsive efforts. This type of apnoea they thought was due to paralysis of the respiratory center from oxygen want and persisted until 15 seconds after the heart had started again, whereas the first kind was a response of the respiratory center to blood which had been to some extent overventilated and was therefore low in CO_2. They thought they were able to shorten the period of apnoea with 5-per-cent CO_2 in oxygen, but not to abolish it. In their paper they published only a schematic representation of polygraph tracings of the pulse and respiration and from these it seems that what they call short periods of asystole lasted from 40 to 65 seconds and the long periods lasted from 70 to 90 seconds. Asphyxial breathing seems to have appeared in about 30 seconds only in the long periods of asystole. This is quite different from the breathing observed and recorded in our case, partly on account of the method of recording and partly on account of probable differences between the two patients in the ability to ventilate between the periods of asystole.

In March, 1936, Jezer, Master and Schwartz (25) reported electrocardiographic studies of the dying heart in two cases. In each there were recurring episodes of stand-still of the heart associated with dyspnoea and hyperpnoea followed by tachycardia and apnoea. They obtained no records of respiration in their cases and they accept the explanation put forth by Hill and MacKinnon of the respiratory irregularities they observed. They warn against large or continuous doses of epinephrine.

SUMMARY

In summary, then, records are presented showing the respiratory irregularities which occur in a patient with ventricular asystole. These records reveal close similarity to those which have been produced in laboratory animals by lowering and raising arterial pressure in the carotid sinus or by sudden obstruction and release of cerebral blood flow. One or both of these mechanisms seems to be responsible for the changes in respiration produced by asystole. Alterations in O_2 or CO_2 tension of the arterial blood or in its hydrogen-ion concentration do not afford an explanation of the changes in respiration caused by asystole.

Carotid sinus respiratory reflexes produced by changes in arterial pressure have not previously been pointed out in human beings. This recently discovered mechanism must be considered as an active factor in governing the respiration of man.

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SALMONELLA SUIPESTIFER INFECTION IN MYOMAS OF THE UTERUS

Report of a Case

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Salmonella suipestifer is becoming recognized as a pathogenic agent of considerable importance for man. While this "hog cholera" bacillus was originally considered the cause of swine fever because it was found in the tissues of as many as 45 per cent of pigs with the disease, hog cholera itself is now generally accepted as due to a filterable virus (Savage (1) 1929). In the last several years numerous outbreaks of food poisoning have been described as due to Salmonella suipestifer, the organism having been recovered from contaminated pork, veal, pastry, etc. that had been ingested, and frequently from the feces of the patients (Clayton and Milne (2), Griffin (3), and others). In some of the earlier reports it was called the paratyphoid C bacillus. In the last few years, in addition to the enteritis caused by the organism, many cases of suipestifer septicemia with typhoid-like clinical picture have been reported (Kuttner and Zepp (4) and others). Also a few cases of pyarthrosis and osteomyelitis caused by this organism have been described (Gajźagó and Göttche (5); Weaver and Sherwood (6)).

Within the Salmonella group are many strains with slight serologic differences (Nabarro, White, Dyke and Scott (7)). Several others besides S. suipestifer have been described as causing food poisoning (S. enteritidis, S. aertrycke, S. Newport). According to Savage (8) Salmonella food poisoning, including the various above types, is the commonest form of food poisoning in England.

In the literature we have found three reports associating Salmonella infection with disease of the female generative organs. Roth (9), in 1928, reported the case of a 21-year-old girl, who was delivered by

a midwife, and was submitted to manual extraction of the placenta. Four days later chills and fever began, and the patient became quite ill and anemic. Cultures from the cervix showed Gram-negative

FIG. 1

motile rods. Later in the illness an empyema of the chest developed, from which was cultured Salmonella suipestifer, as proved by agglutinations. The organism from the cervix showed the same cultural reactions as S. suipestifer, but agglutination tests were not performed.

The patient slowly recovered. The author thought the Salmonella suipestifer infection was of puerperal origin. Biddle (10), in 1935, described the case of a 40-year-old woman on whom an operation was performed for an apparently infected ruptured ectopic gestation. After five days the wound suppurated, and fever and chills appeared. She slowly recovered over a period of six weeks. Blood cultures first taken six days after operation showed S. suipestifer. Whether this was a postoperative complication or whether the original pelvic infection was due to S. suipestifer was not known. Brown (11), in 1935, reported a case of double pyosalpinx due to Salmonella Newport. The patient was 26 years old and had never been pregnant. Her only symptoms were backache, fever and lower abdominal tenderness for 18 days. At operation a pyosalpinx on each side was drained. The patient slowly recovered. Clinically, the condition appeared to be tuberculous. Cultures showed Gram-negative motile rods with cultural characteristics of the Salmonella group. After daily subcultures for three weeks, agglutination was positive for Salmonella Newport.

In this paper we wish to present a case of prolonged septicemia from S. suipestifer, associated with extraordinary abscesses within myomas of the uterus.

CASE REPORT

The patient was a 36-year-old colored woman, who was admitted to the hospital complaining of a tumor mass in her lower abdomen for 8 months, and of a slight cold, sore throat, vomiting, diarrhoea and urinary frequency for five days.

Examination: T. 101.4°, P. 110, R. 24, Hgb. 92%, W.B.C. 10,000. The patient was dehydrated and weak. The nasal mucous membranes were congested, the throat was injected and moist râles were heard at the base of the left lung. Slight tenderness was present over the left kidney and bladder. The fundus of the uterus was replaced by an adherent nodular tumor rising half-way to the level of the umbilicus.

The Wassermann reaction was positive. A catheterized specimen of urine showed numerous white cells, and a culture of the urine revealed B. coli.

Palliative treatment was instituted for the respiratory and urinary tract infections. After eight days cystoscopy was performed. The bladder appeared diffusely injected. The ureters were not catheterized. Following this procedure the temperature rose to 105.6°. Blood cultures showed S. suipestifer, as proved by agglutination. Urine culture again showed B. coli. The temperature gradu-

ally subsided, to rise a week later to 105.4°. At this time there was definite evidence of bronchopneumonia. Three other blood cultures showed S. suipestifer, but later cultures were sterile. Several transfusions were given, and there was a long course characterized by low grade fever.

One hundred and eleven days after admission laparotomy was performed by Doctor Thomas S. Cullen. Numerous adhesions were found about the nodular uterus. One subserous nodule was densely adherent to the transverse colon (see fig. 1). In freeing this nodule a cavity present within the myoma was entered and several cubic centimeters of grayish yellow purulent material were evacuated. A culture was taken. It was necessary to sacrifice a part of the outer coat of the bowel wall to free the suppurating myoma. The lumen was not entered. Supravaginal hysterectomy was performed and the abdomen drained. Convalesence was uneventful except for some drainage from the incision, and the patient was discharged well.

Cultures from the abscess showed a motile Gram-negative rod, which fermented the sugars of paratyphoid B. While there was some agglutination with both the paratyphoid B and suipestifer sera, in neither case was it strong enough to identify the organism. Unfortunately, the organism was not subcultured over a period of several weeks for repeated agglutination tests.

Pathology. The nodular fundus of the uterus measured 13 x 9 x 7 cm. There were adhesions over the surface, beneath which the nodules had a slightly yellowish appearance. On the superior surface over one nodule 4 cm. in diameter was a roughened area containing several small irregular sinuses. On section these sinuses led into an abscess cavity which almost completely replaced a small myoma. The abscess contained yellowish purulent material and had a thick ragged greenish-yellow lining. There were many other myomas through the wall, varying from 2 to 4.5 cm. in diameter, the centers of most of which were occupied by the same greenish-yellow necrosis. A few of the myomas, however, had the usual typical glistening white appearance. The uterine cavity was 7 cm. long and lined with thin gray endometrium.

The microscopical sections showed that the many necrotic appearing myomas were largely hyalinized about the margins, but the centers contained polymorphonuclear cellular debris. Surrounding the undulating hyalinized borders a most intense chronic inflammatory reaction was seen, made up of plasma cells, round cells and foam cells. Within the inflammatory areas between the myomas were many minute abscesses containing polymorphonuclear leucocytes. This inflammation surrounded the myomas and had infiltrated through the uterine wall. There were a few scattered large giant cells here and there between the diffuse round cells and plasma cells. Small groups of cells contained bright yellowish brown granular pigment. Also, there were a few scattered crystals of bilirubin, of the typical brownish yellow star-like granules. As the uterine cavity was approached, the inflammation became less intense, so that beneath the endometrium were only a few areas of collections of round cells. The endometrium

itself was covered by two or three layers of columnar cells, and had a dense cellular stroma, containing a few scattered round cells and plasma cells. The glands were tubular, non-secreting and many were greatly dilated. With the Brown-Brenn bacterial stain no organisms were found in sections of the uterus.

A case of prolonged Salmonella suipestifer septicemia is presented to add to the clinical and pathological picture of an infection that is being recognized as not uncommon. In this case the unusual chronicity was probably due to the abscesses in the myomas of the uterus acting as foci for re-infection.

The appearance of the uterus on section was quite unusual. The myomas had greenish yellow necrotic centers. Doctor T. S. Cullen states that he has never seen such changes in myomas of the uterus studied in the laboratory of this clinic. The surface of one myoma was densely adherent to the bowel wall. S. suipestifer is known as a common cause of food poisoning, and it is possible that the infection extended through the bowel wall in the area of the single dense adhesion. However, it is difficult to see how all the other myomas would have the same degree of necrotic appearance if the condition arose from extension through the bowel. The illness began with upper respiratory infection, gastro-intestinal and urinary symptoms, and it is possible that the patient had food poisoning. However, the original source of the infection was not determined.

The other interesting although also inconclusive reports summarized from the literature indicate that probably this bacillus is to be considered as an etiological factor in disease of the female generative tract. The course would seem to be moderately chronic, but the mortality does not appear to be high.

SUMMARY

A case of Salmonella suipestifer infection associated with abscesses in myomas of the uterus is reported. It seems likely that this bacillus may be a cause of infection in the female generative tract.

Note: This case is listed among a large series of Salmonella suipestifer infections recently reported by A. M. Harvey (*Archives of Internal Medicine*, in press).

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HEMOPHILIC PSEUDOTUMOR: DIAGNOSIS, PATHOLOGY AND SURGICAL TREATMENT OF HEMOPHILIC LESIONS IN THE SMALLER BONES AND JOINTS

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Howell (1) has defined hemophilia as "a condition characterized by a delayed clotting time of the blood and a history of repeated bleedings, which is found only in males and is transmitted by a sex-linked character." Although all of the various factors concerned in the coagulation of hemophilic blood have been studied, no definite departure from the normal has been ascertained (2, 3, 4, 5, 6). No excess of anticoagulant substance has been conclusively demonstrated (1). To remedy this as yet unknown defect in the hemophilic blood structure, several putative therapeutic measures have been introduced, among which may be mentioned the use of blood transfusion (7, 8), placental extract (9, 10), snake venom (11), vitamin C (12), and foreign protein shock (13). But whatever clinical adjuvant may be used and whatever beneficial quality it may possess, the surgery of the hemophilic individual still presents a formidable problem. The solution of such a problem in one individual has been accomplished by the employment of modern electrosurgical technique and this has evolved fresh diagnostic and pathologic conceptions of hemophilic bone and joint lesions.

J. C. (Unit No. 68925), aged 16, a white unmarried male, of Spanish descent, was admitted to the surgical service of the Johns Hopkins Hospital on May 5, 1936, complaining of a painful swelling of the right thumb.

Family History: The mother, living and well, aged 43, has three sisters and no brothers, with eight male children and two female; all without evidence of any tendency to excessive bleeding.

The father, living and well, aged 43, has two brothers and two sisters, with seven male and ten female children; all without evidence of a tendency to excessive bleeding. No history of grandparents is available.

Siblings: 1. Our patient.

2. Manuel. Died in 1930 with tetanus, aged 9. There was a history of frequent and prolonged epistaxis, with an early tendency toward the formation of bruises following slight trauma. At the age of 6 he bled for 25 days from a laceration at the tip of his tongue. Blood studies at this time indicated a clinical state of hemophilia.

3. Felix, aged 10. Normal clotting time.

4. Angel, aged 9. Normal clotting time.

Past History: The patient's birth and development were normal. He had whooping cough at the age of 2 months and measles at the age of 12 years. A review of the systems was negative. His mental development was normal.

Hemophilic History: Aged 2. Laceration of chin. No bleeding.

Aged 4. Tendency to bruise easily. Left ankle became swollen and blue for a period of 3 weeks—a spontaneous hemarthrosis.

Aged 5. Bitten by a "mad dog," with development of a large hematoma. Given 25 injections of rabies antitoxin.

Aged 8. Laceration of inner canthus of left eye. Bled for 21 days.

Aged 13. Laceration of right cheek. Bled for 15 days. Fell out of tree. Hematoma of tongue and submandibular tissues developed in 48 hours. Mouth could not be closed. Tracheotomy contemplated. Treatment with "ovarian extract" and resolution of hematoma in about 21 days. Has been taking similar medication since that time.

Aged 15. Hematuria for 14 days.

Present Illness: His brother stepped upon the base of the patient's right thumb about eighteen months previously, and immediate swelling of this extremity occurred. X-ray examination a week later showed no alteration in bony structure. The swelling gradually spread anteriorly to involve the thenar eminence and distally to involve all but the tip of the first phalanx. During the past three months there has been a rapidly progressive increase in the size of the thumb. For one month he has had constant, severe, throbbing pain that is synchronous with his pulse. There is no other history of small bone or joint involvement. Recent x-ray study reported the present lesion as a "bone sarcoma," and elbow disarticulation was advised.

Physical Examination: Temperature 100.0°. Pulse 90. Respirations 20. Blood pressure 120/80. Height, 5 feet 4 inches. Weight 136 pounds.

The patient was a well developed, muscular boy, with black hair, dark skin, and typical Spanish coloring. The facies was anxious and he was complaining bitterly of pain in his right thumb. There was no adenopathy. A small ecchymotic area, 1 cm. in diameter, was present beneath the left side of the tongue. There were several carious teeth. The tonsils were enlarged and cryptic. Examinations of heart, lungs, abdomen, genitalia, and rectum were negative. The bones and joints of all the extremities were negative except for the lesion involving the right thumb. As noted in Fig. I, the entire thumb was involved in a globular, symmetrical enlargement that extended from the metacarpophalangeal articulation laterally and the web space mesially to the nail. It had a curious rubbery,

cystic quality upon palpation but was not especially painful when examined. The skin was shiny, smooth, and uniformly reddish-black in color except for a small area 2 cm. in diameter over the palmar surface where it was hard and black. In this area there was a slow, constant effusion of thick, dark, fluid blood. Motor function was totally lost. Epicritic sensation was diffusely impaired distally and was absent over the practically gangrenous area noted above.

FIG. 1. PHOTOGRAPH OF HEMOPHILIC "PSEUDOTUMOR"
(Photomicrographs by Mr. Milton Kougl)

Hematological Examination: Hgb. 11.6 gm. (80%). R. B. C. 4.1 million. W. B. C. 9,600. Platelets 120,000. Bleeding time 5 minutes. Clotting time (venous blood) 5 hours. Clot retraction time 15 hours. Fragility test normal. Sedimentation test normal. Wassermann negative.

X-ray Examination: Right hand: Destruction of both phalanges and metacarpal of right thumb. Marked peri-articular swelling. Condition suggests new growth. Chest: Heart within normal limits. Lungs clear. Left ankle: Normal.

Clinical Course: The patient was grouped and matched with three blood donors of Group IV (Moss). On May 8, in an effort to control the severe, practically constant pain, it was decided to attempt an aspiration of the contents of this tumor-like mass. The patient had slept only fitfully since admission and, in addition, rupture of the mass appeared imminent. About 2 c.c. of dark, unclotted blood were aspirated with a Number 18 Luer needle. The puncture wound bled continuously for the next twenty-four hours and intermittently for the following

FIG. 2. PRE-OPERATIVE ROENTGENOGRAM

two days. The lesion increased in diameter during this time some 2 cm., became much firmer, and caused almost unbearable pain. Amputation was obviously the procedure of choice, and it was suggested that electrosurgical technique offered the best chance for the control of the anticipated hemorrhage. The operation note follows:

May 11, 1936. Avertin 80 mgm. per kilo. Ether supplement. The entire right forearm and hand were cleaned with iodine and alcohol. The usual drapings

were applied, but no tourniquet was used. As soon as the operative procedure was begun, a transfusion of 500 c.c. of citrated blood was commenced into the left forearm. The small bleeding point from the unsuccessful attempt at aspiration of the clot was immediately coagulated with one application of the electrocautery. Alternating between the scalpel and coagulation terminals of the Bovie unit, the operator outlined an incision around the base of the thumb, carrying the incision rather low on the lateral aspect of the thumb and rather high in the web space. The entire amputation was done with the electrocautery and there was surprisingly little bleeding. There was no capillary ooze. Any of the larger vessels, when encountered, were seized with an artery forceps and successfully coagulated.

After the skin and subcutaneous tissues had been incised, a huge cystic cavity, lined with a rather smooth brownish-red material that resembled the external layer of a subdural hematoma, was entered. This layer, however, did not bleed upon manipulation. It might be noted that, at the moment of incising the cystic cavity, dark fluid blood as well as fragments of what appeared to be blood-clot spurted forth under terrific pressure. A portion of this material was found five feet from the operation field. The cyst extended to the area of bone destruction noted in the X-ray, but there was no evidence of tumor growth. All of the bone appeared to have been destroyed by the pressure of this hematoma, and only a few fragments of calcified material were present. No attempt was made to curette the base of this cyst, although it was thoroughly cauterized with the coagulation current. There was no bleeding to speak of at any time and the field was dry when the defect was closed. The base of the defect was filled in with some muscle tissue and tendinous structures remaining from the dorsal aspect of the amputation stump. The skin was then brought together with a continuous suture of fine silk. Vaseline gauze was applied to the incision itself and the entire extremity was immobilized in a posterior plaster splint. At one time during the procedure the systolic blood pressure fell to a level of 80, probably as a result of the avertin anesthesia.

Postoperative Course: His immediate postoperative course was marked by a complete absence of pain and by no evidence of hemorrhage from the operative site. The variations in clotting time, the presence of fever and tachycardia, the extent of a hematuria that increased in severity postoperatively, are assembled in the chart. On May 18 the blood picture in detail was as given below. It is to be noted that at this time he had developed a mild secondary anemia, attributable apparently to the hematuria.

Hgb. 9.4 gm./100 cc. R. B. C. 3.45 m/cmm. Vol. packed R. B. C. cc./100 cc. 30.5. W. B. C. 8800. Platelets 264,000. I. Index 7.5. Bleeding time 5 min. Clotting time 53 min. Clot retraction time 7 hrs. M. corp. vol. 89. M. corp. hgb. 27. M. corp. hgb. conc. 31. Reticulocytes 2.8%. 100 cells: Seg. neut. 68. Juv. neut. 12. Eosin. 1. Lymph. 16. Mono. 3.

Eight days after operation the first surgical dressing was done. There was some dried and semisolid blood clot beneath the vaseline gauze that had been

placed over the incision. The incision had partially separated, the space being filled by a firm hematoma perhaps 1 cm. in width. The skin over the proximal portion of the thumb was pink and normal looking and showed a great difference from its former appearance. Along the edge of the hematoma the skin showed normal healing and no bleeding was manifest. The wound was dressed with a bland balsam of Peru ointment. On May 28, nine days later, the second dressing was done. There was considerable retraction of the clot, with diminution in the size of the open defect. The skin edges showed progressive healing. There was no hemorrhage or evidence of infection. The wound was exposed to the sunlight every day for an hour from that time until June 8, when healing was complete. On June 1 he complained of pain upon motion of the third finger of the right hand, and examination two days later disclosed a small amount of fluid in the proximal interphalangeal articulation, with definite discoloration on its palmar surface. This disturbance suggested the onset of another acute hemarthrosis. This lesion, however, was quiescent at the time of his discharge.

DISCUSSION

The diagnosis of hemophilic bone and joint lesions depends in large part upon roentgenography of the affected part, and the condition may be suspected even in the absence of evidence pointing to the essential familial defect. Clinically, the acute hemarthrosis of the hemophiliac may be confused with a pyarthrosis. There is distension of the joint space, spontaneous throbbing pain, limitation of motion; there may be a slight elevation of temperature, a mild leucocytosis, and even local heat, although the skin discoloration is characteristically evident in a dusky cyanotic hue. In the more chronic forms the process simulates tuberculosis, arthritis deformans, and Perthes's disease in the case of lesion of the hip-joint. Recent roentgenographic studies of hemophilic lesions in the large joints, some of which have included careful descriptions of the various clinical stages, have been made by Doub and Davidson (14), Engels (15), Key (16), Freund (17) Reinicke and Wohlwill (18), Solis-Cohen and Levine (19), Thomas (20) and Prip Buus (21). On the basis of their roentgenographic studies the authors are in more or less accord in describing, in the acute case, distension of the joint capsule, associated later with opacities in the soft tissues due to iron pigment deposition in the organizing hematoma. In the diagnosis of the later stages of the process the following points have been emphasized: (1) Sharply defined erosions of the joint margins, round or oval in shape, surrounded by a sclerotic zone;

(2) Subchondrally situated rarefactions; (3) Narrowing and irregularity of the joint space; (4) Rarefactions in the osseous tissue unconnected with the joint surfaces, representing hemorrhagic cavities within the bone. In the lesions of long duration complete destruction of the joint surface with subluxation and osseous ankylosis have been reported. The march of events in the small bones has never been ascertained roentgenographically. As Reinicke and Wohlwill state (p. 441): "We also lack roentgenographic studies of changes in the fingers in more patients, especially in those who reveal clinical evidence of bleeding during childhood in an isolated phalangeal joint." In 65 patients, 10 years of age or older, Thomas has noted 15 per cent involvement of the fingers and 2 per cent involvement of the toes, with no permanent deformities. From a perusal of the literature even these figures appear high. In our patient the roentgenographic picture was twice reported as that of a bone sarcoma. It appears, however, to represent the end stage of a traumatic hemarthrosis of hemophilic origin in a small articulation. The spontaneous disturbance in the mid-phalangeal articulation of the third finger of the same hand may represent the onset of a similar process, and its progress will be carefully watched.

Complete comprehension of this deceptive roentgenogram rests upon an understanding of the pathological sequence of events which has previously been ascertained only in large joint hemarthritides. The latter were early described by König (22) and very little has been added to his writings. A careful amplification of his studies, however, has been made in recent years by Freund. Both writers divide hemophilic bone and joint lesions into three stages. The first is that of a simple hemarthrosis with thickening of the synovia, deposition of iron pigment, and villous hypertrophy. The second stage is that of a panarthritis with progressive destruction of the joint capsule, cartilage, and ends of bone by the expanding hematoma, similar to that seen in the presence of an aneurysm or a tumor. The cartilage becomes irregularly necrotic, but most characteristic is the formation of cavities in the bone. These may occur as simple depressions in the articular surfaces or they may be found deep in the cancellous bone. The latter represent in all probability hemorrhages into the bone, the further progress of which has been stopped by the thickness of the sur-

FIG. 3

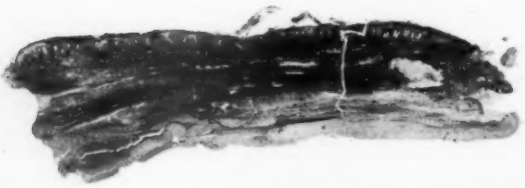

FIG. 4

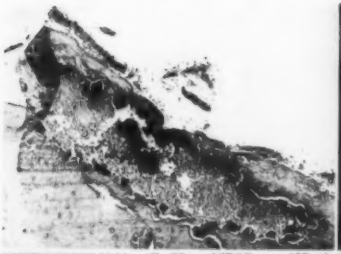

FIG. 6

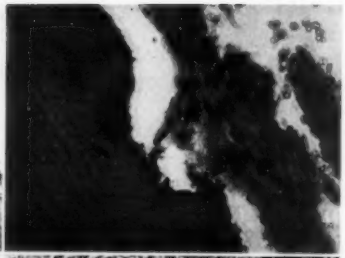

FIG. 5

FIG. 7

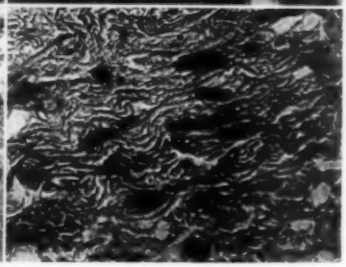

FIG. 3. CROSS SECTION OF SKIN AND UNDERLYING HYALINIZED CONNECTIVE TISSUE, REPRESENTING, EXCEPT FOR DÉBRIS, THE END STAGE OF BONE AND JOINT DESTRUCTION

The corium is heavily infiltrated with fresh and old hemorrhage. Only a small amount of the blood pigment gives the iron reaction with potassium ferro-ferricyanide. Most of this iron appears to be within the macrophages. 6×.

FIG. 4. BONE AND CARTILAGE FRAGMENTS FROM INTRACYSTIC DÉBRIS, SHOWING BONE EROSION AND FORMATION OF LACUNAE SECONDARY TO PRESSURE

At this point there is marked osteoclastic activity. 300 ×

FIGS. 5 AND 6. CHARACTERISTIC LACUNAR EROSION OF BONE. 400×

FIG. 7. IRON PIGMENT DEPOSITION IN HYALINE PORTION OF CYST WALL. 400×

rounding osseous tissue. Reinicke and Wohlwill have advanced the theory that hemophilic blood exerts some as yet unknown chemical effect upon bone, which results in its rapid absorption. There is no evidence in favor of this theory, and the pathological studies in this case tend further to discount it. The third stage, more or less poorly differentiated from the second, has been termed that of "regression," and shows a tendency toward healing, with the production of a pseudoarthritis deformans and with fibrous or osseous ankylosis.

The final stage in a small articulation, as observed in our patient, may not be that of regression, but may be that of complete articular and osseous destruction, leading to actual bursting of the soft tissues and skin. The progressively expanding hematoma cannot be held in control by the weaker joint structures nor can the interosseous hemorrhage be checked by the thin cortex of a phalangeal bone. The microphotographs 4, 5, 6, 7 of the bony detritus in the center of the hematoma give evidence of all stages of the pathological sequence. The eventual cyst wall consists only of skin and a membrane of organizing blood and connective tissue.

Keefer (23) has stated that "under no circumstances should hemophilic joints be treated by surgical methods." An exception must be made to this otherwise sound counsel in cases of peripheral lesions where cutaneous rupture threatens. A surgical attack, however formidable it may appear, must be planned to avert the otherwise greater danger of severe or fatal hemorrhage and of infection which would possibly follow open rupture. Both complications have been observed in individuals previously treated in this hospital. The severe pain endured by our patient likewise demanded relief. As noted in the operative report, the amputation was done with the Bovie electrosurgical unit, both the scalpel and coagulation terminals being used. The procedure was carried out rapidly and uneventfully. Blood loss was minimal, and even more striking was the essentially normal healing process that followed. These results form a decided contrast to the piecemeal tissue ligation and the postoperative bleeding noted in Blalock's case (24).

It is interesting to note that both Poland (25), in 1850, and Ericksen (26), in 1856, found the use of the actual cautery helpful in the control of hemophilic hemorrhage. Custer and Krumbharr (27) have

likewise mentioned the use of electrosurgical technique in an unsuccessful exploratory laparotomy performed upon a hemophilic individual. Hinman (28) has used the electrocautery on one occasion, performing prostatectomy upon a hemophiliac, with the aid, however, of many transfusions. With these exceptions we can find no discussion in the literature of the use of electrosurgery in the operative treatment of the hemophiliac. Its value can scarcely be overestimated

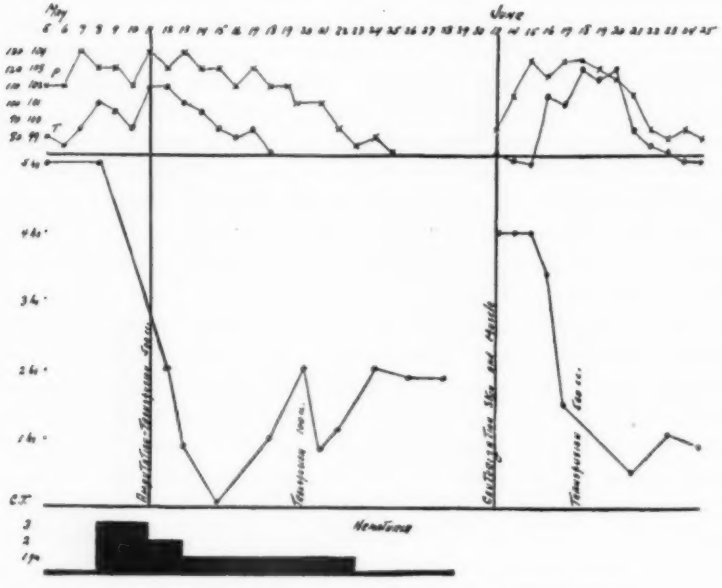

CHART I. VENOUS CLOTTING TIME RESPONSE TO TRANSFUSION AND TO TISSUE CAUTERIZATION

both for major surgical procedures on these patients and for the control of hemorrhage from small lacerations, being much more effective for the latter, for instance, than silver nitrate or Monsell's paste.

The chart shows strikingly the marked reduction in clotting time following the first transfusion, confirming again the observations of Minot and Lee (7). The less marked and poorly maintained reduction in the clotting time following the second experimental transfusion

of but 100 c.c. indicates that the phenomenon has a quantitative relationship to the amount of transfused blood.

The remarkable reduction in clotting time from five hours to five minutes, following the electrosurgical amputation with its attendant prophylactic blood transfusion, suggested the possibility that cauterization of hemophilic tissues in this instance had caused mobiliza-

FIG. 8. POSTOPERATIVE PHOTOGRAPH

tion of thromboplastic substance, in addition to that transferred passively by the transfusion. To test this hypothesis the following experiment was carried out. Thirty-four days after the original operation an area of skin and subcutaneous tissue on the anterior surface of the right thigh measuring 12 cm. by 1 cm. was partially cauterized with the Bovie coagulation unit. On the third day following this

procedure the clotting time by the venous method had fallen from a level of four hours to one of three and a half hours; on the fourth day, readings of one hour and thirty minutes were obtained. At this time, deep muscle hemorrhage from an insufficiently cauterized puncture wound necessitated transfusion, with prompt cessation of the bleeding.

FIG. 9. POSTOPERATIVE ROENTGENOGRAM

The significance of this phenomenon will be made the subject of further study among our hemophilic patients.

SUMMARY

This patient, a hemophilic individual with a clotting time of four to five hours, presented an extraordinary instance of bone and joint

involvement of the right thumb that was twice roentgenographically diagnosed as a "bone sarcoma." This unique lesion represented, however, the end result of hemophilic bleeding into a small articulation and into its adjacent osseous structure, as contrasted with the previously reported instances of similar disorders in large bones and joints. The pathological sequence of events was similar to that taking place in large bones and joints, but instead of regression and eventual ankylosis, in the small bones and joints there may be also progressive destruction and cutaneous rupture. The roentgenographic diagnosis of hemophilic bone and joint lesions must in the future be qualified by these anatomical differences. Amputation of the pseudotumor was successfully accomplished with the electrocautery, and postoperative healing was essentially normal. This technique, with the supplementary aid of blood transfusions, appears to offer a distinct advance in the surgery of the hemophiliac. The favorable influence of cauterization of hemophilic tissue upon reduction of the clotting time has been suggested by the observations in this case and will be made the subject of further study.

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ADENOMA OF PARATHYROID WITH RENAL INSUFFICIENCY

Case Report

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In 1905 MacCallum (1) reported the case of a 26-year-old man, who died of renal insufficiency and in whom, at post-mortem, a parathyroid adenoma was found. The author speculated at that time whether there might be some relationship between the renal disease and the adenomatous parathyroid.

Since then numerous reports have appeared of cases showing the combination of renal insufficiency and hyperparathyroidism. That general parathyroid hyperplasia may occur in certain patients with renal insufficiency seems undoubted. Pappenheimer and Wilens (2) examined at autopsy the parathyroid glands of 27 patients who had died of renal insufficiency, and found that the mean weight of the parathyroids was significantly increased in the forms of nephritis showing renal lesions diffuse and severe. When one finds diffuse parathyroid hyperplasia in association with chronic renal changes, there may be doubt as to which of the two conditions represents cause and which effect. However, as pointed out by Castleman and Mallory (3), in patients having a parathyroid adenoma or adenomatous areas in two parathyroid glands, it seems most reasonable to consider such changes as neoplastic. If renal changes then are found in association with parathyroid neoplasm, they should be considered as either secondary to the hyperparathyroidism or as totally coincidental findings. The association of renal disease with adenomata of the parathyroid seems far too common to be merely a coincidental finding. Albright and his co-workers (4) have especially emphasized this point of view, and have suggested that the mechanism of renal impairment may occur in two forms. Their type I is renal insufficiency secondary to pyelonephritis in association with renal stones.

That renal stones are present in a considerable proportion of patients with parathyroid adenomata has been proved by the Massachusetts General Hospital group of workers, and chronic renal insufficiency secondary to this cause is readily understandable. However, their type II renal insufficiency does not seem quite so clear cut a pathological entity. They postulate calcium and phosphorus concretions in the renal substance leading eventually to inflammatory changes, sclerosis and contracted kidneys. Regardless of the mechanism of the production of this type of renal lesion in association with hyperparathyroidism, a clinical picture which is indistinguishable from secondary contracted kidneys is commonly seen in such patients. Elsom, Wood, and Ravdin (5) stress the point, however, that in cases of chronic renal disease of this type secondary to hyperparathyroidism, changes in the optic fundi are rare, and the blood pressure is usually not elevated. Our patient, we believe, falls into this second group; for with removal of the parathyroid tumor and relief from the symptoms of hyperparathyroidism, he showed a most surprising improvement in renal function.

Case report (J. H. H. U. 66042): F. K., aged 45, a white male school teacher was admitted to the Johns Hopkins Hospital on November 11, 1935, and discharged December 21, 1935. His chief complaints on admission to the hospital were loss of weight and strength, severe pains in the arms, back, and legs, nausea, vomiting, and soreness of the eyes. There were no data of importance in the family history.

The patient stated that he had the "usual childhood diseases" but could not recall them specifically. At the age of 21, associated with a series of attacks of sore throat and chronic nasal catarrh, there had developed rather severe bronchial asthma. For the relief of this the tonsils, adenoids, and nasal polyps were removed. The asthma improved somewhat but had continued in a less severe but chronic state to the time of admission. The constant use of stramonium cigarettes seemed to give the only satisfactory, though temporary, relief. From childhood to the time of admission the patient had suffered from periodic attacks of indigestion. At infrequent intervals he would be free from digestive disturbance for several months at a time. At other times he would have to take a large dose of bicarbonate of soda after almost every meal to allay a very distressing heartburn. In spite of these two chronic conditions the patient considered himself an unusually strong and vigorous person, and the state of his health was in no wise a concern to him.

It is difficult to ascertain accurately just when the present illness began. Two and one-half years before admission to the hospital, while on an automobile trip to Florida, the patient developed distressing pain in the lumbar region, which

radiated down the back of both legs. A diagnosis of sacro-iliac strain and sciatica was made. After several months of this trouble, without specific treatment, the severe pain disappeared, but milder "cramping pains" in the calves of both legs, the feet, and the toes persisted. These were never very severe and never caused any curtailment of accustomed activity. When the pains were sufficiently disturbing, ten grains of aspirin brought quick relief. In March, 1934, the patient was ill with what was apparently severe lobar pneumonia. During convalescence the pains in the back, legs, and feet were more severe than they had ever been. Convalescence was slow and tedious but by mid-summer 1935 he had recovered sufficiently to return to his duties as a teacher, though pain had not completely left him.

In March, 1935, the condition became conspicuously worse. The first changes occurred in the digestive system. The appetite became poor and a weight loss, amounting to 25 pounds by the time of admission, began. Generalized abdominal pain, severest in the epigastrium, followed almost every meal and often reappeared before more food was taken. Enormous doses of soda were necessary to afford relief; and when this failed, the induction of vomiting was necessary. The patient became weak, restless, sleepless, and depressed. The pains in the back and legs became almost constant and about six weeks before entering the hospital, they spread to the muscles of the thorax and upper extremities. Fifty to sixty grains of aspirin supplemented by three or four grains of codeine daily were necessary to render the pain tolerable, and to allow him to obtain sleep. During the day the patient massaged his muscles constantly, as he found some relief from pain by this procedure. Two weeks before admission to the hospital the weakness and pain made it necessary for him to have assistance in rising from a chair. Three days before admission, vomiting became almost continuous; so that no food and little or no water was retained. For about a month before admission his eyes had been red and swollen, and made uncomfortable by exposure to the light.

Physical Examination: Temperature 98.6°; pulse 65; respirations 20; blood pressure 155/100; weight 118 pounds; height 5′8½″.

General Appearance: The patient appeared desperately ill. He was restless, irritable and obviously in great pain. His face was greyish in color and the mucous membranes were pale. He retched frequently and whenever he took a sip of water it was almost immediately vomited. The breathing was slow but typically asthmatic in type with prolonged, labored expiration. Audible wheezing was obvious. There was marked emaciation and obvious recent weight loss of considerable extent. The skin was dry and the subcutaneous fat was wasted. There was no oedema.

Bones, Joints, and Muscles: There was marked wasting of all the muscles. This was associated with generalized muscle weakness and atonia. The muscles of the arms and legs were all sensitive to pressure. There were no gross abnormalities in any of the joints and no apparent tenderness of any of the long bones. There was diffuse tenderness over the lumbosacral region and over the gluteal muscles. The hamstring muscles and the sacrospinalis muscles were badly con-

tracted though not spastic, and they limited the degree of forward flexion of the lumbar spine to about one-third its normal movement.

Eyes: The eyes were deep-set and expressionless. There was considerable swelling and pigmentation of the periorbital tissues. There was bilateral moderately severe episcleritis. The pupils were equal and regular and reacted to light. The extra-ocular movements were normal.

Ocular Fundi: The media were clear. The discs were sharply outlined and of normal color. There were no exudates or hemorrhages and the arteries were not abnormal.

Nose: There was no obstruction, discharge, or evidence of bleeding.

Mouth: The mucous membranes and tongue were quite pale. There were complete upper and lower dentures. There was no abnormal pigmentation. The tonsils had been cleanly removed and there was no infected pharyngeal lymphoid tissue.

Lymph Nodes: No enlargement.

Thyroid Gland: The gland was not enlarged and no nodules could be felt.

Chest: The chest was emaciated but there was slight increase in the anteroposterior diameter. The movements were symmetrically restricted. There was no abnormality in the fremitus. The percussion note was everywhere resonant, and the breath sounds were vesicular. Throughout both lungs there were numerous coarse, sonorous rhonchi but no crepitant râles.

Heart: There were no shocks or thrills over the precordium. The heart and aorta were not enlarged. The sounds were of normal quality; there were no accentuations and no murmurs. The cardiac rhythm was regular.

Pulses: The pulses were equal and of normal volume. The radial arteries were moderately thickened and tortuous but no actual beading of the walls was discernible. There were pulsations in the vessels of the feet of normal intensity.

Abdomen: The abdomen was flat and freely movable. There was no ascites. The muscles were not rigid, but the patient complained of slight diffuse tenderness and resisted palpation slightly. The liver, spleen, and kidneys were normal in size, and no abnormal mass was felt.

Genitalia: Normal.

Rectal Examination: No hemorrhoids. The prostate was of average size and there were no indurated areas. No abnormal mass was felt.

Neurological Examination: Except for weakness the station seemed normal. Pain made locomotion very difficult, but there was no apparent ataxia. There were no demonstrable lesions of the cranial nerves. All the skeletal muscles were wasted, weak, and atonic, but there was no localized abnormality. The tendon reflexes were all present, brisk and equal, and there were no abnormal reflexes. There were no paraesthesias and no sensory abnormalities.

Laboratory Examinations:

Urine: Clear straw, specific gravity 1.010; albumin one plus, sugar negative, microscopic; very occasional w.b.c., r.b.c., and thin hyaline casts. No Bence Jones protein.

Blood Count: Hemoglobin 72%; r.b.c. 3.62 million, w.b.c. 7,700. The differential formula was normal. There was some microcytosis but little poikilocytosis, and the red blood cells appeared of normal color. There were no regeneration forms seen and no abnormal leukocytes. The platelets appeared present in normal numbers.

Blood Wassermann Test: Negative.

Blood Chemistry: Non-protein nitrogen 80 milligrams per cent; fasting sugar 84 milligrams per cent; bromides absent; CO_2-combining power 58 volumes per cent; serum chlorides 83.8 milliequivalents; spectroscopically negative for sulphaemoglobin.

Phenosulphonephthalein: First hour 10%. Second hour 5%.

Gastric Test Meal: No free HCl. either before or after 0.5 mgm. of histamine.

Stool: Benzidine negative for blood. No parasites or ova were seen.

X-rays:

Chest: Lungs clear; heart and aorta normal in size and shape.

Stomach: Persistent deformity of the duodenal cap associated with five and twenty-four hour retention indicating the presence of a chronic duodenal ulcer.

Spine: Lumbar spine normal.

Skull: No abnormality in the density of the bones.

Kidneys: Small group of calcified bodies in the left side of the abdomen possibly due to stones in the left kidney.

Long Bones: Increased osteoporosis of the tibiae, femora and bones of the forearms.

Course in the Hospital: The patient was in wretched condition. Even small quantities of water were immediately vomited and he could retain little or no food. His insomnia and restlessness were extreme and pain was almost constant. For the relief of these he required huge doses of aspirin, codeine, and sedatives. The temperature remained normal, and the pulse rate varied only slightly. Breathing was constantly labored due to bronchial asthma. The physical findings changed but little except that the episcleritis advanced rapidly and became distressingly uncomfortable.

No satisfactory explanation for the clinical picture presented by the patient was immediately suggested. It was apparent that the most urgent problem was that of the grave renal insufficiency. It was thought that the persistent vomiting might have so lowered the serum electrolytes as to depress the kidney function. Accordingly large quantities of sodium chloride and fluids were given, and though the serum chlorides rose to a normal figure, the patient grew subjectively worse, and the blood non-protein nitrogen remained practically stationary. Serum base determinations were not made. Finally, seven days after admission to the hospital the diagnosis of hyperparathyroidism was suggested. The serum calcium was then found to be 19.3 milligrams per cent. and the inorganic phosphate 4.3 milligrams per cent. These figures were twice confirmed, and the diagnosis of hyperparathyroidism seemed clearly established.

Preparations were immediately made for operation and on November 27, 1935, the patient was transferred to the surgical service of Dr. William F. Rienhoff.

Operation: The operation was performed under avertin, gas, and oxygen anaesthesia. The usual collar incision as for a thyroidectomy was made. When the cervical fascia was split and the right lateral lobe of the thyroid was retracted medially, the mass came plainly into view. It was a yellowish, cystic tumor of about the size of an English walnut. The tumor was dissected free and delivered with no difficulty after the operator had first determined the presence of parathyroid tissue on the opposite side.[1] Approximately four-fifths of the tumor was removed.

Description of the Tumor: Sections showed numerous large clear cells arranged in an adenomatous formation. These cells possessed clear, slightly stippled pale pink cytoplasm and large round or ovoid very clearly outlined nuclei. Their

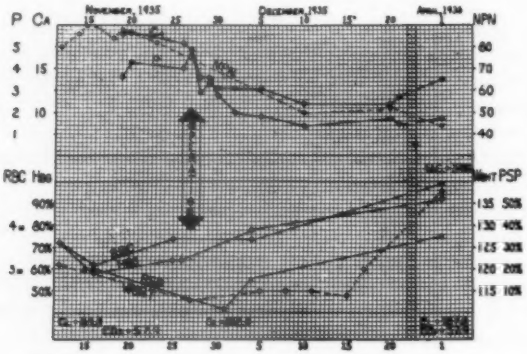

CHART I. SHOWING THE IMPORTANT LABORATORY DATA AND THE CHANGES WHICH OCCURRED AFTER REMOVAL OF THE PARATHYROID TUMOR

chromatin was evenly dispersed in small granules. The acini forming the tumor were lined with one or, at the most, two rows of cells arranged in radial formation. Elsewhere the tumor cells grew in sheets and cords between rather thin-walled blood vessels. No oxyphilic cells were seen, the growth having arisen entirely from the chief cells.

Postoperative Course: The patient stood the operation remarkably well. He was tremendously encouraged by at last having his long and puzzling illness adequately explained and an operation successfully performed. As can be seen from Chart I, on the day of operation the serum calcium was 17.3 milligrams per cent. and the inorganic phosphate 5 milligrams per cent. Thereafter, the level of

[1] Since the patient was quite ill, no time was wasted in attempting to identify all the parathyroid glands.

both these constituents fell rapidly to normal, and two weeks after the operation the blood non-protein nitrogen had fallen to 50 milligrams per cent. Little change, however, occurred in his blood count or 'phthalein excretion. He continued to be very weak, though his appetite improved somewhat, and he was able to be out of bed a few hours a day. Almost immediately after the operation the pain began to lessen, and this improvement, though slow, was progressive. The condition of his eyes, on the other hand, grew steadily worse and was a constant and painful annoyance. The urine did not change, and at the time of discharge was still of very low specific gravity and contained a trace of albumin, a few red blood cells and hyaline casts. On December 17, 1935, the general physical condition

PHOTOGRAPH OF PATIENT IN DECEMBER, 1935, MADE SOON AFTER DISCHARGE FROM THE HOSPITAL

PHOTOGRAPH OF THE SAME PATIENT IN MARCH, 1936, MADE FOUR MONTHS AFTER REMOVAL OF THE PARATHYROID TUMOR

had improved sufficiently to allow the patient to return to his home. He was instructed to spend the greater part of the day resting and to gauge his activity by the subjective improvement. He was urged to attempt to gain weight, and was allowed a liberal diet, the protein content of which was limited to approximately 80 grams daily. No treatment was advised other than massage and such analgesics or sedatives as were necessary to control the rapidly diminishing pain.

Interval Note: The patient improved slowly but steadily after returning to his home. Almost at once he began to increase his activity so that three months after the operation he was able to take a three or four mile walk without discomfort. His appetite improved amazingly; so that in a little more than three

months he gained twenty pounds. For a time, at the beginning of increased physical activity, there was oedema of the ankles, but this symptom rapidly disappeared. The very distressing eye condition cleared up completely within a month after the operation. The diffuse bone and muscle pains, while not completely subsiding, became much less intense. Most of the remaining pain seemed to be different from that formerly present. The knees, small joints of the hands and the left hip were sore and stiff in the morning. For several weeks before returning to the hospital the patient suffered somewhat from his old digestive discomfort. His chronic asthma continued as formerly. On March 31, 1936 he returned to the hospital for a check-up.

Physical Examination: Temperature 98.6°; pulse 90; respirations 22; blood pressure 145/80; weight 140 pounds. The extraordinary improvement in the patient's general appearance is best appreciated by referring to the two photographs. He literally looked like a different person, and several members of the staff failed to recognize him. There was excellent nutrition and he was mentally alert, bright, and cheerful. His movements were quick and spontaneous and not accomplished with the apparent overpowering fatigue which had characterized everything he did on his previous admission. The intense inflammatory condition in his eyes had completely subsided. His greatest discomfort resulted from the asthma, not in the least improved since the previous admission. The remaining physical findings were normal and need no further comment.

Laboratory Examinations:

Urine: Clear, s.g. 1.020; acid reaction. Sugar negative, albumin negative. Microscopic: rare r.b.c. and w.b.c. No casts.

Blood Counts: Hemoglobin 99 per cent (14.4 grams). Red blood count 4.55 million; white blood count 7,000. The smear and differential formula were normal.

Blood Chemistry: Non-protein nitrogen, 44 milligrams per cent.; urea nitrogen, 28 milligrams per cent.; serum chloride, 107.8 mill./eq.; CO_2-combining power, 52.2 volumes per cent.; serum calcium, 9.3 milligrams per cent.; serum inorganic phosphate, 3.5 milligrams per cent.; total serum protein, 6.0 grams per cent.

Phenolsulphonephthalein: First half hour, 18 per cent.; second half hour, 12 per cent.; second hour, 5 per cent.; total, 35 per cent.

Range Specific Gravity of Urine: 1.015–1.024.

Urea Clearance Test: (1) 32 per cent. normal standard; (2) 34 per cent. normal standard.

Gastric Test Meal: (Alcohol 70 cc. 7 per cent.): Free HCl, 0; Total HCl, 8. 15 minutes after 0.5 mg. histamine: Free HCl, trace; total HCl, 20.

X-rays: Stomach: No filling defect seen in either stomach or duodenum. Long bones: Distinctly less porosity of bones than on previous examination.

DISCUSSION

Our patient, we believe, falls into that group suffering from hyperparathyroidism and chronic renal disease which is secondary to it.

When he was first seen by us, frank renal insufficiency was present. There was an elevated non-protein nitrogen, extremely low phthalein excretion and a fixed low specific gravity of the urine. Although we felt at the time that some of the renal insufficiency might be due to the marked dehydration and loss of electrolytes which were secondary to the patient's vomiting; yet when hydration was re-established in the hospital after a period of 16 days, prior to operation, the non-protein nitrogen, phthalein and specific gravity did not improve at all. As a matter of fact there was only the barest improvement in these three factors during the post-operative convalescence of three weeks in the hospital, despite marked symptomatic betterment in every way. However, during the thirteen weeks interval before a return for a check up, a considerable change for the better in renal function had taken place. His non-protein nitrogen had fallen slightly to 44 milligrams per cent, phthalein excretion was now 35 per cent in two hours, and the urine could be concentrated to a specific gravity of 1.024.

The single other patient that the authors have observed, who had hyperparathyroidism in association with this type of renal insufficiency, had a blood non-protein nitrogen of 80 milligrams per cent at the time of operation, and although she showed considerable improvement in symptoms and general well being after removal of the tumor, she failed to show any improvement in renal function. When last seen, three years after operation, her non-protein nitrogen was still over 70 milligrams per cent. Chemical and clinical evidence of hypoparathyroidism was still present at this time. It seems important to point out here that the removal of the parathyroid adenoma apparently rendered the renal lesion stationary; for it would be most unusual for a patient with this degree of renal insufficiency from any other cause to remain essentially stationary over a three year period. Other patients have not shown improvement of renal function comparable to that shown in our patient, in so far as we are aware. Bellin's (6) patient was suffering from renal insufficiency when first seen, with a blood urea nitrogen of 58.4 milligrams per cent, phthalein excretion 5 per cent in two hours and urine specific gravity 1.009. When seen four months after operation there was most marked clinical improvement with gain in weight and the amazing disappearance of calcium deposit in the ear drums which had made the patient deaf.

However, there was no corresponding improvement in the kidney function, in fact there seemed to be slowly increasing azotemia, the last determination of the urea nitrogen having been 81.5 milligrams per cent. But one must point out here that at this last observation the serum calcium was reported to be 14 milligrams per cent and the phosphorus 7.3 milligrams per cent. The possibility that another parathyroid adenoma was present in this patient seems highly likely.

Elsom, Wood, and Ravdin's (5) well studied case showed some improvement in renal function after removal of the parathyroid adenoma. Prior to operation her blood urea nitrogen varied between 37 and 31 milligrams per cent, specific gravity was fixed at 1.010 and urea clearance was 18–27 per cent. Eleven months later her blood urea nitrogen had fallen to 24.4 milligrams per cent, the specific gravity remained fixed at 1.010, and the urea clearance had risen to 36 per cent.

One of Albright's (4) patients, a little girl of 13, before operation had a low phthalein, non-protein nitrogen 55–66 milligrams per cent, and a low specific gravity. Two months after removal of the parathyroid adenoma there had been no demonstrable improvement in the renal function.

Previous experience with renal insufficiency, other than that due to pyelonephritis or renal calculi, secondary to hyperparathyroidism, seems to be less hopeful than that with the patient under consideration. There is no explanation apparent to us for the improvement in kidney function which has taken place in our patient, to a greater extent than in previously reported cases. One might assume, purely on theoretical grounds, that generalized nephrocalcinosis was the cause of the renal insufficiency, and that such a process at certain stages of its development may be reversible. While it is recognized that the renal insufficiency associated with blood electrolyte imbalance may persist for some time, it does not seem reasonable to explain upon this basis the remarkable changes in renal function observed in our patient.

Another feature of considerable interest in our patient was the remarkable eye condition. The ophthalmological consultants were quite unfamiliar with any previous association of episcleritis with hyperparathyroidism, and the only reference to any suggestively

similar condition that we have found is that of Bellin (6). The chronicity of the lesion in our patient and its prompt improvement after operation leaves but little doubt that the two conditions occurred with more than a coincidental relationship. In future cases of obscure episcleritis, calcium and phosphorus studies may throw additional light upon this unusual feature of our case.

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LUPUS ERYTHEMATOSUS ASSOCIATED WITH VISCERAL VASCULAR LESIONS

A Series of Autopsied Cases

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Under the title of "A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis)," Baehr, Klemperer and Schifrin (1) have reported a remarkable series of 23 autopsied cases of lupus erythematosus disseminatus of which 20 showed widespread visceral vascular lesions.

These lesions were of several types. Certain areas, such as the skin, showed capillary dilatations and extravasation of blood and serum. Many capillaries, arterioles, and venules showed endothelial proliferation, often associated with thrombosis. Many small vessels showed degenerative and necrotizing changes, frequently with thrombosis and haemorrhage. Thirteen cases of the 23 showed endocarditis of a coarse verrucous type differing markedly from rheumatic verrucae, unaccompanied by clinical and anatomical evidence of rheumatic fever and tending to resemble the atypical endocarditis of indeterminate etiology described by Libman and Sachs (2). Glomerular lesions were conspicuous in 18 cases. Most commonly the glomerular capillaries showed hyaline thickening, which produced an appearance of rigidity not unlike the contours of a wire loop. The lesions were accordingly designated "wire loop lesions." In 2 cases diffuse glomerulonephritis occurred. In 3 cases, segments of glomeruli were implicated by proliferative or necrotizing changes. Vascular lesions were occasionally found in the myocardium, lung, liver, pancreas, spleen, and ovaries. Six cases showed involvement of all viscera.

The clinical course was characterized by prolonged irregularly remittent fever, involvement of serous membranes including synovia, depressed function of bone marrow (3) (leukopenia, thrombopenia,

anaemia), and by clinical evidence of vascular changes in the skin, kidneys and other viscera. The cutaneous lesions appeared as erythematous macules or blotches which tended to become confluent in the form of a butterfly across the nose and cheeks, and which also involved the lip, chin, chest, back, extremities and digits. Sensitiveness to sunlight was common. The buccal mucosae were also affected. Arthralgia, with synovial effusion or ankylosis, and signs of pericarditis and pleuritis were frequently observed. Signs of renal damage were common and were occasionally well marked. Ophthalmoscopic abnormalities (4) were seen in 2 cases. Although the clinical appearances were not incompatible with those of an infectious disease, bacteriological studies were inconclusive or negative.

Most remarkable was the sex incidence of the disease. Of the 23 cases reported, 22 were women. The one male included in the series had atypical cutaneous lesions and no visceral lesions. This observation is strikingly confirmed by our own experience.

The age incidence was likewise noteworthy. Of 22 cases in females, 18 were in the second and third decade of life.

These data, which have been extensively quoted from Baehr, Klemperer and Schifrin, combine to form a well rounded, consistent and clearly demarcated clinical complex. It was with great interest, therefore, that the records of this department were examined, with the object of surveying the accumulated facts and formulating a comparison with those quoted above.

The 15,000 autopsies recorded include about 7,500 patients over the age of 13 years. Approximately 35 per cent of the adults were negroes. Five cases of lupus erythematosus were found, one of which was in a negress. Only one patient was of the male sex. The ages ranged from 18 to 48.

Case 1. Colored woman, aged 35 (Autopsy No. 7486) (5). Lupus erythematosus with arthralgia, myalgia, and fever; terminal infection; vascular lesions in kidneys.

For two years the patient had had recurrent arthralgia and myalgia. Nine months before her death the arthralgia underwent marked exacerbation; the ankles became swollen, red and tender. Later the joints of the upper extremities were involved and an eruption appeared in the skin of the face and elbows. Irregular fever was present. Examination revealed general tenderness of muscles and of joints. Over the nose, cheeks, elbows and scapular spines there was a con-

fluent, dry, scaly eruption with a tendency to atrophic scarring. Both ankles were tender and edematous. The cervical, axillary and epitrochlear lymph nodes were enlarged. For six weeks the patient had continuous irregular fever. The skin lesions became somewhat more extensive. Death occurred with delirium and signs of bronchopneumonia. Haemoglobin 60 per cent, red blood cells, 3,500,000, white blood cells 6,600. Urine negative. Wassermann negative. Biopsy of lymph node showed chronic non-tuberculous lymphadenitis.

Anatomical Diagnosis: Clinical history of lupus erythematosus. Great enlargement of axillary, retroperitoneal, pelvic and inguinal lymph nodes. Localized tuberculosis of a lymph node. Bronchopneumonia. Multiple abscesses in muscles, subcutaneous tissues and kidneys. Old pleural and pericardial adhesions. Sacculated accumulation of fluid in pericardium. Slight arteriosclerosis.

The kidneys showed moderate enlargement and contained numerous abscesses in which staphylococci were found. Microscopically, in addition to abscesses, there was hyaline thickening of many glomerular afferents and of portions of occasional glomeruli. Frequently the thickened walls of the glomerular capillaries took the haematoxylin rather than the eosin stain. Some of the glomeruli were finely scarred. Sclerotic arterioles were seen in the adrenal and pancreas. The anatomical evidence of tuberculosis was limited to a single cluster of tubercles in one of the subpectoral glands; these tubercles were partly fibrous and partly caseous. Except for these none of the sections showed lesions of tuberculosis. The lung was likewise free from tuberculosis.

The next case does not belong in the group under discussion. The distribution of the lesions and their history suggest that they may have been of the discoid variety rather than genuine acute disseminated lupus erythematosus. It is interesting also that the patient was the only male in the series and was the oldest in the series by a full decade. Although doubtful, the case is included herewith for completeness and interest.

Case 2. White male, aged 48 (Autopsy No. 7884). Lupus erythematosus (discoid type ?). Extensive vascular lesions in kidneys. Albuminuric retinitis. Cardiac hypertrophy.

For 4 years the patient had had nycturia. For 3 months he had had progressive dyspnea accompanied by nausea, anorexia, palpitation and epistaxis. Vision had been dim for 3 weeks. Examination showed emaciation, pallor, haemorrhagic and exudative retinitis, cardiac enlargement, hydrothorax and marked hypertension. There was a scaly eruption over the tip of the nose and on the ears. A dermatologist stated that the lesions were probably those of lupus erythematosus but a frost-bite lesion could not be ruled out. Death occurred with signs of lobular pneumonia.

Anatomical Diagnosis: Chronic diffuse nephritis; acute exacerbation. Cardiac hypertrophy. Albuminuric retinitis. Ascites. Hydrothorax. Confluent lobular pneumonia. Lupus erythematosus (?).

At autopsy the kidneys were found to weigh 120 and 125 grams. The capsules were adherent to a rough, finely scarred, dark red surface, sprinkled with slightly elevated gray-brown nodules averaging 1 mm. in diameter. There were areas of gray opacity in the cortex. The striae were distorted. Microscopically, the kidneys showed many large dense scars including mononuclear cells and hyaline obliterated glomeruli. There were many casts in tubules. The smaller arteriolar branches showed intimal thickening, often with obliteration of the lumen. There was much fat in the glomerular epithelium, in the walls of the glomerular vessels, and in the tubular epithelium. There was striking reduplication of the elastica in smaller and medium-sized arteries. The eye showed choroidal arteriolosclerosis, albuminuric retinitis with flat detachment, and hyaline and fatty masses in the retina. On the skin of the ear the epidermis was markedly atrophic and was thrown up into great folds. In many places the papillae were obliterated. The blood vessels appeared intrinsically normal but were surrounded by extensive perivascular infiltrates. Except for arteriolosclerosis in the pancreas the other organs showed no vascular lesions.

Case 3. White female, aged 38 (Autopsy No. 11465). Lupus erythematosus. Vascular lesions in kidneys. Haemolytic streptococcus septicaemia. Lobular pneumonia. Abscess in rectus muscle. Acute splenic tumor.

The patient said she had had rheumatic fever 9 years previously. A cutaneous eruption had appeared in the spring of each year for the last 4 years and had gradually receded. The present attack, the fourth and severest, began as a little spot on the nose and spread over the cheeks, neck, ears, palms and legs. A tender area appeared on the roof of the mouth. Fatigue and headaches were present persistently. Examination showed an erythematous and scaly eruption on the areas mentioned. On the hard palate there was an ulcer 4 cm. in diameter. The tonsils were covered with small patches of exudate. There was slight hypogastric tenderness. Haemoglobin 60 per cent. Red blood cells 3,700,000. White blood cells 2,440. There was irregular fever. The cervical nodes became tender. Petechiae appeared on the back. The nose and fingers became quite tender. There was pronounced and increasing albuminuria and cylindruria. Beta haemolytic streptococci were twice cultivated from the blood. The leukocyte count increased to 21,000. The abdomen became tender and rigid. This was followed by delirium and death.

Anatomical Diagnosis: Lupus erythematosus. Diphtheritic laryngitis and tracheitis. Haemolytic streptococcus septicaemia. Lobular pneumonia. Peritonitis. Abscess in rectus muscle. Acute splenic tumor.

The kidneys were soft and red and weighed 200 grams each. The external surfaces were flecked with haemorrhage. Microscopically, many of the glomerular afferents were thick and hyalinized. There were one or more hyaline loops in

individual glomeruli. Blood was found in occasional tubules. The other viscera were devoid of vascular lesions.

Case 4. White female, aged 18 (Autopsy No. 12961). Disseminated lupus erythematosus. Vascular lesions in kidneys. Necrosis and edema of retina. Lobular pneumonia. Pneumococcus septicaemia.

Four months before her death the patient developed a skin lesion which spread rapidly over the nose, cheeks, trunk, back and extremities and began to involve the hard palate, gums, and sublingual mucosa. Five weeks before death there was a generalized convulsive seizure followed by temporary blindness. Ophthalmoscopic examination revealed areas of retinal degeneration. There was irregular fever. Signs of pulmonary consolidation appeared. Haemoglobin 62 per cent. Red blood cells 2,400,000. White blood cells 3,400 to 14,500. Urine contained a trace of albumin and occasional casts. Phthalein excretion 90 per cent.

Anatomical Diagnosis: Lupus erythematosus disseminatus. Ulcerative stomatitis, laryngitis and pharyngitis. Esophagitis. Septicaemia (pneumococcus IV). Focal necroses in spleen. Acute splenic tumor. Focal inflammatory areas in kidneys, with necrosis; slight acute nephritis. Necrosis and edema of the retina.

Rather numerous glomeruli showed slight lesions involving isolated capillary loops. In these there were little fibrin thrombi, and in some areas a few necrotic cells and an occasional leukocyte. In a few places there was slight proliferation of the tuft epithelium. Many capillaries in the glomerular tuft were thick and hyalinized; their walls took the eosin stain strongly and thus were conspicuous. They greatly resembled the "wire loop lesions." In one area in the kidneys the small vessels showed mononuclear infiltration in their walls; there were inflammatory areas with necrosis in the neighborhood. These suggested focal areas of inflammation rather than interstitial nephritis. A few haemorrhages were found in the tubules.

Several sections of skin showed no definite lesions. There were some areas of round-cell infiltration in the subcutaneous tissue; in other areas scales had formed on the keratinized epithelium. One area showed a vesicle. Other areas showed necroses in the lower layers of the epithelium.

There was one little focus of necrosis in the retina with an accumulation of little round masses suggesting colloid droplets. In a few places there were accumulations of fluid in the lower layers of the retina. No haemorrhages were seen.

Case 5. White woman, aged 40 (Autopsy No. 14514). Lupus erythematosus disseminatus. Widespread vascular lesions in the kidneys, liver, gallbladder, colon, pancreas, heart, brain, knee and vertebra. Verrucose endocarditis (non-rheumatic). Thrombi in cerebral vessels. Areas of encephalomalacia.

The patient had had weakness, arthralgia, malaise for more than three years before her death. The joints which pained most were those in the back and shoulders. Fifteen months before death several small papular lesions appeared on

the right cheek. During the next 6 weeks these spread and became confluent, covering the nose and both cheeks and including the chin, forehead and arms. The eruption was accompanied by burning and itching and by continued pains in the joints. The cutaneous eruption receded and repeatedly recurred. The patient also had abdominal and costal pain and diarrhea. She had edema of the ankles and sterile effusions in the chest and abdomen. Great emaciation supervened. Some of the joints became stiff. There was slight general enlargement of lymph nodes. Many of the skin lesions became infected. The conjunctivae were inflamed and the lips were swollen. There were many superficial ulcers in the diffusely inflamed buccal mucosa. Haemoglobin 105 to 60 per cent. Red blood cells 4,000,000. White blood cells 5,440 to 10,360. Wassermann negative. Slight to moderate albuminuria. Blood protein 5.3 per cent. Blood culture negative. Patient died with signs of lobular pneumonia.

Anatomical Diagnosis: Lupus erythematosus disseminatus. Inflammation and widespread hyalinization of small arteries and arterioles in liver, gallbladder, colon, pancreas, kidneys, heart, brain, knee and vertebrae. Verrucose endocarditis. Small scars in myocardium. Area of necrosis in myocardium; mural thrombus in left ventricle; infarct in kidney. Area of encephalomalacia. Minute thrombi in cerebral vessels. Subacute glomerulonephritis. Lobular pneumonia. Hyperplastic bone marrow. Extensive pleural and pericardial adhesions.

There were old pericardial adhesions. Along the line of closure of the mitral valve there were firm partly organized non-friable verrucous lesions varying between 0.5 mm. and 3 mm. Several of these verrucae were attached to the valve by thin thread-like pedicles. The edges of the valve and the chordae tendineae appeared unaltered. On one cusp of the aortic valve there was a tiny verrucous nodule. There was a myocardial scar, and a small mural thrombus on the left ventricle. The kidneys were of normal size. One showed an old infarct. The renal surfaces were smooth. The striae were straight.

The endocardial verrucae consisted of fibrin, fibroblasts and round cells. The underlying valve tissues were extensively infiltrated with mononuclear leukocytes, plasma cells, and fibroblasts. No bacteria were demonstrable in sections specially stained.

In the kidneys occasional arterioles were surrounded by round cells and were conspicuously hyalinized. The glomeruli exhibited widespread alterations, most of which were of mild degree. These lesions included hyalinization and thickening of one or more loops in any one glomerulus. Other glomeruli contained masses of pink-stained hyaline thrombus material. A few glomerular afferent vessels were hyalinized. A number of hyaline casts were present. The medium-sized and large vessels were sclerotic. In the colon arterioles were found to be necrotic and surrounded in part by an inflammatory exudate. Inflammatory and degenerative lesions were also found in the other regions mentioned in the anatomical diagnosis. Many of the cerebral vessels contained thrombi. Areas of distinct encephalomalacia were seen in the cortex and in the cornu Ammonis. There were no vascular lesions in the eyegrounds.

DISCUSSION

The first patient was a negress (6), aged 35, who had had recurrent arthralgia and myalgia for 2 years. During the last 9 months of this period the joints were especially painful and moderately widespread lupus erythematosus disseminatus appeared. During the last 7 weeks irregular fever was present. The illness closed with an intercurrent infection. The anatomical findings were complicated by evidence of the final infection. Vascular lesions were not prominent and were virtually limited to the kidneys.

The second patient was the only male in the series and was older than the others. His inclusion in this study is open to question, since it is possible or even likely that he had the discoid type of lupus. Autopsy disclosed chronic nephritis with acute exacerbation, cardiac hypertrophy and albuminuric retinitis.

The third patient, a woman aged 38, had had four annual attacks of disseminated lupus erythematosus. She had leukopenia prior to the onset of the streptococcus infection which ended her life. Marked albuminuria and cylindruria were observed. Vascular lesions in this case were not prominent and were limited to the glomeruli.

The fourth patient was a girl, aged 18. She had an acute type of disseminated lupus erythematosus which spread uncontrollably and in the space of four months attained almost universal distribution. Anaemia and definite leukopenia were present. A convulsive seizure five weeks before death was succeeded by transient amaurosis. The illness ended with a pneumococcus infection. There were widespread inflammatory and degenerative lesions in the kidneys. Many of the glomerular capillaries had the thick hyaline eosinophilic appearance of the "wire loop lesions." The retina showed areas of necrosis and edema.

The fifth patient, a woman aged 40, had had weakness, malaise and arthralgia beginning 3 years before death. During the last 15 months there were recurrent attacks of disseminated lupus erythematosus, with abdominal pain, pleural and abdominal effusions, hypoproteinemia and albuminuria. There was no azotemia. The illness produced marked emaciation and ended with pneumonia. Vascular

lesions were conspicuous, advanced and very widely disseminated in the kidneys, liver, gallbladder, pancreas, heart, brain, intestine, knee, and vertebrae. Many of the small cerebral vessels contained thrombi. There were small areas of encephalomalacia. There was verrucous endocarditis of atypical structure unaccompanied by lesions of rheumatic fever (7).

Of the five patients in this series the second may be dismissed from consideration, since the cutaneous lesions were open to question. One additional case, omitted from the foregoing description, may have been either pellagra or lupus erythematosus, and in view of the uncertainty has been likewise ruled out. The remaining four were all women; the ages were 35, 38, 18 and 40 years, respectively; the duration of illness varied between 4 months and 4 years. In the first and fifth case the cutaneous symptoms did not appear at the onset of the disease. All the cases were characterized by general constitutional disturbances such as fever, arthralgia, myalgia, serous effusion, anaemia, leukopenia, and evidence of kidney disease. One patient had a convulsive seizure and amaurosis. All four cases ended with intercurrent infection which in each instance was limited to the closing days or weeks of the patient's life.

In the last two cases there were conspicuous vascular lesions. In the last case these lesions were very widely disseminated through the viscera, including brain and bones. The extensiveness and severity of these lesions preclude the possibility that they might be due to terminal infection. The long duration of the cutaneous changes would certainly exempt them from such an explanation.

The clinical course and especially the fever suggest that the disease is due to infection. The identity of this infection is a mystery. Bacteriological studies were fruitless. There was no clinical or anatomical evidence of rheumatic fever or syphilis.

The evidence collected tends to confirm the observations of Baehr, Klemperer and Schifrin. While the present series of cases taken by itself is too small to warrant any conclusions, the two series taken together suggest that lupus erythematosus—especially in acute cases—represents merely the cutaneous expression of a generalized vascular disease. The general agreement as to the character of the vascular

lesions in the various cases would seem to exclude the possibility that these cases represent a mere coincidence of lupus erythematosus and visceral vascular disease.

In this connection it is interesting that Volk (8) has reported an autopsied case of lupus erythematosus disseminatus and periarteritis nodosa occurring in the same individual.

Since the cause of lupus erythematosus is unknown it is obviously impossible to state whether all of the cases are identical etiologically.

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PLATE 1

(Photographs by Mr. Milton Kougl)

Fig. 1. Case 5. Artery in colon, partly necrotic, with inflammatory exudate. × 100.

Fig. 2. Case 4. Glomerulus showing hyaline loops and fibrin thrombi. × 390.

Fig. 3. Case 5. Branch of hepatic artery in portal field of liver. The wall of the vessel is partly necrotic and is surrounded by a cellular exudate. × 200.

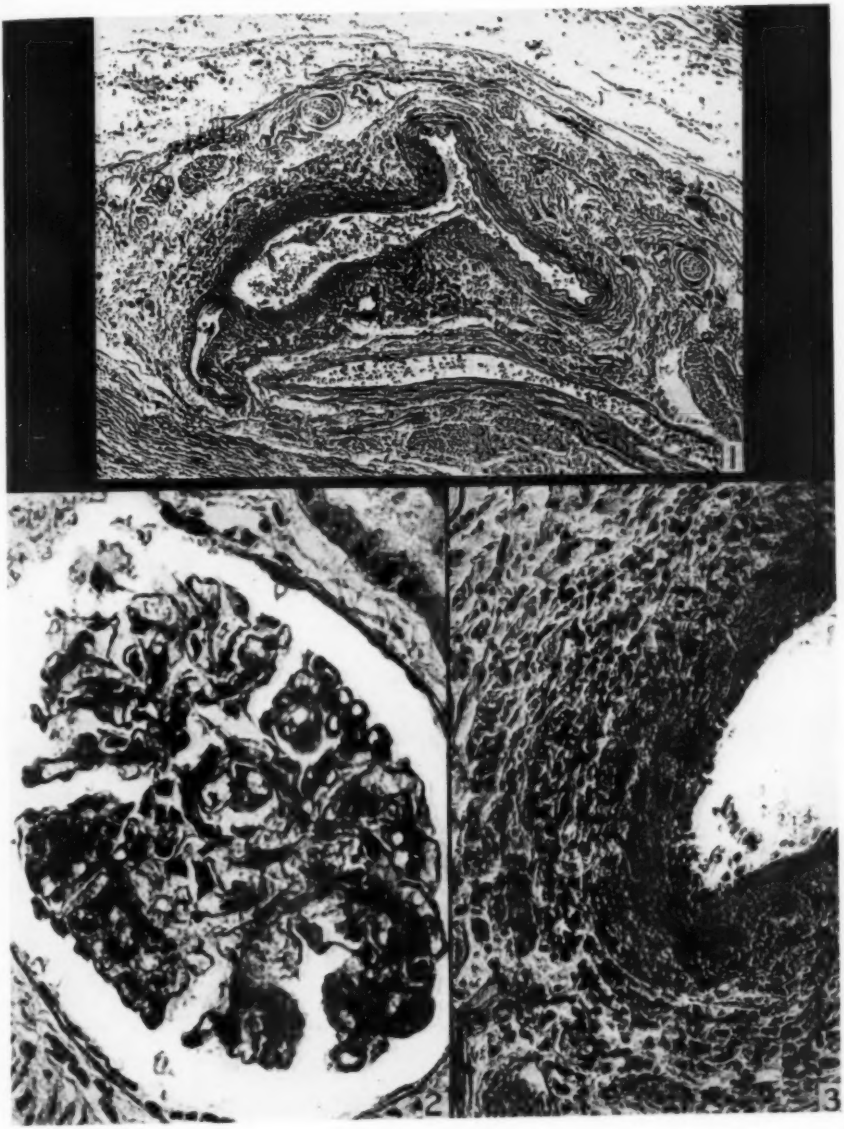


PLATE 2

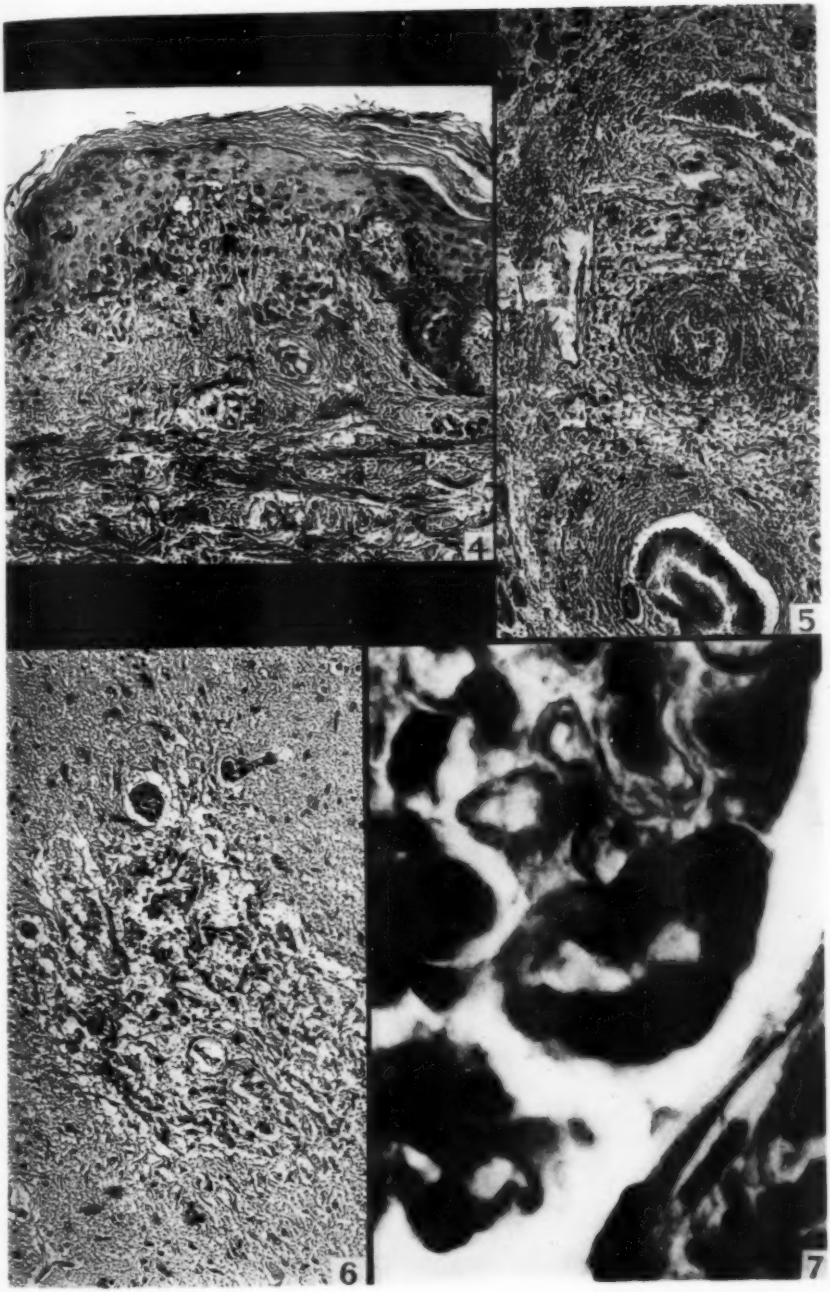
(Photographs by Mr. Milton Kougl)

FIG. 4. Case 5. Skin from epigastric region of abdomen. The epithelium is desquamating. The papilla is swollen and densely infiltrated by a cellular exudate. × 100.

FIG. 5. Case 5. Inflamed branch of hepatic artery in portal field of liver. × 100.

FIG. 6. Case 5. Area of encephalomalacia. At the upper part of the lesion a small thrombosed capillary is seen. × 100.

FIG. 7. Case 5. In the centre of the figure there is a large thick hyalinized glomerular loop resembling the "wire-loop" lesions described by Baehr, Klemperer and Schifrin (see text). × 1150.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STEATORRHOEA WITH UNUSUAL INTESTINAL LESIONS

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Progress in the diagnosis and treatment of disease is necessarily dependent on the gradual accumulation of data, the recognition of similarities, and subsequent classification. Of the three closely similar cases which form the basis of the present communication, the first was published nearly thirty years ago, and the second appeared thirteen years ago. To these is now added the author's case. The three cases thus collected appear to represent a single morbid process.

In 1907 Dr. George Whipple (1) reported from this Department a case of "A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues." The patient was a physician, aged 36 years, who had had recurrent arthritis for five years, also cough, mucopurulent expectoration, and progressive emaciation. During the last six months of his life he had tenderness and enlargement of the abdomen and fatty diarrhea. Examination gave evidence of arthritis and anaemia. A few purpuric spots and a fading patch of erythema nodosum were also found. The haemoglobin was 52 per cent, red blood cells 3,930,000, white blood cells 6,780 to 8,180, eosinophiles 3 to 9 per cent. The stools were white and creamy and contained large numbers of fatty acid crystals and many globules of neutral fat. Analysis of the stool showed neutral fat 50 per cent and fatty acids 30 per cent.

The autopsy findings, in brief, were as follows:

Anatomical Diagnosis: Neutral fat and fatty acid deposits in intestinal mucosa, mesenteric and retroperitoneal glands and thoracic duct; chronic lymphadenitis; anaemia; emaciation; organizing peritonitis, pleuritis, pericarditis and aortic endocarditis; cardiac dilatation and hypertrophy with fatty degeneration; bronchopneumonia and edema of lungs; caseous apical scar and tuberculous bronchial lymphadenitis.

Intestine: The jejunum is dilated, and shows a velvety swollen mucosa flecked over with little pin-point yellowish grains which seem to be intimately connected with the mucosa, in some cases beneath it. No ulcerations are seen. The Peyer's patches in the ileum are not conspicuous.

Mesenteric glands present a most remarkable appearance. They are greatly enlarged and rather elastic to the touch. On section the glands are found to be of an opaque pale-yellowish color, with almost complete disappearance of the gland tissue. There is an indefinite translucent reticulum, through which one sees minute grains of opaque yellow color. These are thickly sown throughout all the glands. The glands on section bulge beyond the capsules. A similar condition is seen in the glands at the root of the mesentery in the neighborhood of the pancreas.

Microscopical Findings

Jejunum and ileum: Frozen sections show deposits of fat in the villi and submucosa. Fatty acid crystals show up very clearly as rosettes of needles. The majority of the masses (of fat) fill the spaces in which they lie, but some only partly do so, the rest of the space being filled with a fine coagulum suggesting lymph. Some of these spaces in the villi contain a fine spider-web-like reticulum of coagulated material in which may be embedded a few mononuclear cells or a small droplet of fat. A lining endothelium can often be made out in such cases.

Sections stained with haematoxylin and eosin show very conspicuous vacuoles, many of which contain a finely granular pink-staining reticulum. Some of these vacuoles are lined by endothelial cells, giant polynuclear cells, and large mononuclear foamy cells. Other vacuoles are surrounded by a dense capsule of fibrous tissue.

Lymph Nodes: Unstained frozen sections show refractile fat globules and great numbers of long acicular fatty-acid crystals. Marchi preparations show even more fat than was found in the intestine. Giant cells are numerous and closely applied to the margins of the fat deposits.

No lesions were found in the pancreas.

After the report by Whipple no strictly comparable case appeared in the literature for sixteen years. In 1923 Blumgart (2) reported "Three Fatal Adult Cases of Malabsorption of Fat." The three patients presented steatorrhea, anaemia with high color index, and pronounced emaciation. At autopsy one (Case 2) showed chylous ascites. In this patient the intestinal mucosae were of light yellow color; the loose connective tissue in the submucosa contained numerous large mononuclear cells and multinucleated giant cells with finely vacuolated cytoplasm. These cells were believed to contain fat. The pancreas was normal. None of the patients in Blumgart's

series had disease of the serous membranes similar to that found in Whipple's case.

In the literature which has appeared during the thirteen years since Blumgart's report, I have been able to find no case genuinely comparable to the foregoing. The following case, however, is almost identical in detail with the first one cited, and is markedly similar to that of Blumgart.

Unit No. 56715. The patient was a white man, aged 37 years. During the previous 15 years he had had repeated attacks of arthritis, usually of mild degree. Nine weeks before admission to the hospital he sustained a fracture of the wrist; this was followed by a severe and widespread recurrence of the arthritis. Several infected teeth were then extracted and the articular symptoms were beginning to subside at the time of the patient's admission to the hospital.

In addition to the skeletal disorder, the patient had been afflicted with digestive disturbances. Two years before there had been a week of painless jaundice. For at least two years the patient had noticed post-prandial discomfort and meteorism; this was accompanied or succeeded by watery diarrhea. The stools numbered four to six each day, and tended to be especially numerous after the ingestion of rough vegetable foods. There were also transitory exacerbations of abdominal distress, with meteorism, weakness, palpitation, and dyspnoea. Despite this, the appetite was little impaired, although the patient feared to aggravate his symptoms by excessive eating.

Physical Examination: The patient was a thin man with a dark complexion. There was general pigmentation, most marked near flexures in the skin. There was neither exophthalmos nor impairment of ocular movement. The pupils were equally and normally reactive. The teeth were in very bad condition. The axillary nodes were slightly enlarged. There were a few palpable nodes in the anterior, cervical and supraclavicular regions. The epitrochlear nodes were not palpable. The thyroid gland was not enlarged. There was scoliosis of the spine. There were no abnormal findings referable to the heart and lungs. The abdomen was slightly prominent, soft, and doughy. No masses were palpable, nor could the liver and spleen be defined. There were no signs of ascites. The genitalia and the nervous system showed nothing abnormal.

An orthopedic surgeon found "Marked scoliosis of the lower dorsal and upper lumbar regions to the right, with marked rotation. Moderate bilateral coxa vara. Marked callus formation about the site of Colles' fracture at right wrist. Swelling of right arm with stiffness and limitation of motion in all joints of fingers and wrist. Moderate swelling of both knees. Passive motion in all joints fairly good. Marked crepitus in left knee."

The arthritis improved but the gastro-intestinal symptoms increased in severity and the body weight continued to diminish. The stools were watery and pale, and regularly contained occult blood. There was steady decline in the haemoglo-

bin percentage and in the number of erythrocytes. On the day before death the stool contained a quantity of dark red blood. Rectal examination, previously negative, now showed two small nodules in the anterior rectal wall; these were believed to be polyps. On the next day the patient died.

Blood count: July 16, 1934 (nine weeks before death), haemoglobin 70 per cent, red blood cells 4,500,000, white blood cells 12,000. September 21, 1934 (day of death) haemoglobin 30 per cent, red blood cells 2,000,000, white blood cells 7,000. Wassermann negative. Agglutination of B. melitensis and B. dysenteriae negative. Blood sugar 75 mgm. per cent. Non-protein nitrogen 40 mgm. per cent. Van den Bergh test negative.

Stools: Liquid, gray, consistence similar to that of creamy pus. Microscopically, only a few leukocytes and erythrocytes were found. Repeated search always failed to show parasites or ova. Benzidine and guaiac tests always strongly positive. Cultures of stool negative for bacteria of the colon-typhoid group.

Gastric analysis:

Fasting:

Free hydrochloric acid	none
Total acidity	20
Benzidine positive	

After histamine:

Free hydrochloric acid	100
Total acid	113
Benzidine positive	

Barium enema: No obstruction; sigmoid rather narrow; caecum perfectly smooth; no evidence of carcinoma. Gastro-intestinal fluoroscopic examination: normal stomach and duodenum; entire large intestine very spastic; no evidence of any ulcerative lesion. Intracutaneous tuberculin test 1:1,000–negative.

Glucose tolerance test:

	mgm. per cent
Fasting	80
½ hour after 60 gms. glucose	96
1 hour	105
2 hours	110
3 hours	100

Sucrose tolerance test:

	mgm. per cent
Fasting	75
1 hour after 60 gm. sucrose	86
2 hours	102
3 hours	95

Bromsulphthalein test of liver function: No retention after 30 minutes.

Urine: Specific gravity 1.015–1.027. Benedict test for sugar gave a slightly green color to the urine. No albumin. Occasional leukocytes. No bile or urobilin. Temperature varied from 99° to 101°, with a brief elevation to 104°.

Autopsy No. 13858; thirteen hours after death.

Anatomical Diagnosis: Fat accumulation in villi of ileum and in mesenteric lymph nodes, with multinuclear giant-cell reaction. Rheumatism. Rheumatic vegetations on mitral and tricuspid valves. Aschoff bodies in myocardium. Pericardial adhesions. Chronic arthritis, interphalangeal and carpal. Pulmonary oedema. Pleural adhesions.

Abstract of Autopsy Records: The peritoneal surfaces are smooth. The caecum is distended. Beginning at a level approximately 20 cm. below the duodenojejunal flexure the mucosa of the jejunum appears roughened and pitted in scattered poorly circumscribed areas, intervening areas being normal. The mucosa of the ileum is dull and granular-looking, with opaque yellow material between the transverse folds, evidently covering the villi. The mucosa of the intestine for the greater part of its length shows this same yellow opaque material. Lower down it becomes covered with mucus but no distinct ulcerations can be seen. The mucosa of the colon looks normal. There are some small ulcerations in the lower part of the rectum just above the anal orifice. Otherwise the mucosa looks normal. The feces discovered in the small intestine are dark brown and liquid; those found in the large intestine are gray and pultaceous, with distinct bile staining, and are not bloody or tarry.

The mesenteric and retroperitoneal lymph nodes are unusually large and prominent, many attaining the size of 2.5 cm. The nodes are invariably discrete and firm, with no caseation or calcification. In many nodes the gray cut surfaces are mottled by fine yellow punctate markings.

Microscopical Notes

Jejunum: The mucosa is moderately well preserved. The stroma contains a large number of mononuclear wandering cells, plasma cells, polymorphonuclear leukocytes, vacuolated macrophages resembling foam cells, and occasional giant cells. These cells occur in the tunica propria and in the submucosa, mononuclear types being numerically preponderant. The cells of Paneth are well preserved. The most conspicuous change consists in the presence of innumerable large spaces in the deeper layers of the tunica propria. These spaces, many of which are large enough to be seen with the naked eye, are associated with broadening and blunting of the villi. By the haematoxylineosin stain the spaces appear empty. Many are seen to be lined by endothelium. The muscularis mucosae and the muscularis are relatively thin. The serosa has been removed (artefact). Bacterial stains show the presence of gram-positive cocci, gram-negative bacilli, and a few gram-positive bacilli in the lumen. Fat stains are described below.

Ileum: The mucosa is poorly preserved. At several points it is covered by small collections of amorphous necrotic material in which a few pyknotic mononuclear leukocytes are found. In other respects the changes are identical with those found in the jejunum, except that the distinctive spaces are slightly smaller and less numerous. The lymphoid follicles appear normal. Bacterial stains show the

presence of small numbers of gram-positive cocci and occasional bacilli having the stippled appearance of diphtheroids and situated in the lumen.

Transverse Colon; Stomach: No lesions are found.

Rectum: In a few areas the mucosa is lacking. In other areas it is covered by necrotic material containing large numbers of mononuclear leukocytes and macrophages, as well as occasional fibroblasts. At a few points fibrin is seen. The submucosal connective tissue is increased. A few mononuclear infiltrations are seen between the muscular layers and in the subserosa.

Mesenteric Lymph Nodes: The mesenteric lymph nodes contain innumerable microscopic and macroscopic spaces and clefts; the largest of these evidently correspond with the yellow punctate markings observed in the gross at the time of autopsy; many are bordered by endothelium and hence are interpreted as greatly enlarged lymphatics. No normal-sized lymphatics are found. Wherever peripheral sinuses are recognizable they also are seen to be greatly enlarged. The cells in the pulp are chiefly mononuclear and plasma cells, with a minority of vacuolated macrophages and multinuclear giant cells. In many instances the multinuclear giant cells lie in close proximity to the large lymphatics previously described. Many of the giant cells are shown to contain fat. Bacterial stains are negative.

The nodes most affected are those at the root of the mesentery and those near the head of the pancreas. A node from the ileocaecal region shows dilated sinuses and many lipophages but none of the huge lymphatic spaces found elsewhere.

Special Stains: Zenker-fixed material embedded in paraffin was used for the haematoxylin-eosin and bacterial stains previously mentioned. For frozen sections formol-fixed material was embedded in gelatin; this method was used for Sudan and Scharlach R stains, also for the nile-blue sulphate, Smith-Dietrich, and Schultz cholesterol methods. The Ciaccio stain was carried out on formalin-fixed tissue, which was subjected to chromates in the usual manner.

The Scarlach R and Sudan III stains showed that the large spaces in the intestine and lymph nodes contained masses of fat. For the most part this fat was not lost during the staining procedures. Fat was likewise demonstrated within many mononuclear cells and within giant cells. With the nile-blue sulphate stain most of the material in the lymphatics stained blue; a few areas were stained pink. With the Smith-Dietrich stain these areas stained gray-blue to black; much of the lipoid material was removed. With the Ciaccio method followed by Sudan III a few small areas were stained red. In sections tested by the Schultz cholesterol method (3) a few areas gave the blue color indicative of cholesterol (4). This was confirmed by the polariscopic examination, which likewise showed a few small areas of double refractility.

Note by Dr. MacCallum: There is distinct evidence of rheumatic infection in the heart; Aschoff bodies are demonstrated in the myocardium. The vegetations on the mitral and tricuspid valves are quite typical rheumatic vegetations. The mucosa of the ileum shows the most peculiar change in that the villi of the

mucosa are greatly enlarged and contain large fat globules which were doubly refractive and are now surrounded by large cells with granular cytoplasm. It is suggested that these may be the lymphatic channels in the villi and the same suggestion is made for the great accumulations of fat in the lymph nodes of the mesentery where they seem to be surrounded by endothelial cells. The very striking feature is the presence of giant cells in relation to these fat masses. The whole nature of this process is obscure. It apparently corresponds precisely with that described by Dr. Whipple (1).

Perusal of the foregoing data makes evident the great clinical similarity and the virtual anatomical identity of the three cases cited. The patients, aged 36, 44, and 37 years, respectively, had prolonged steatorrhea with anaemia, marked emaciation and debility. Leukocytosis was uniformly absent. The stools in one case contained 80 per cent fat. In no case did the stool have the voluminous foamy appearance typical of sprue, and in no case were ova or parasites found.

Anatomically, all three cases showed unusual and dense deposits of fat throughout the length of the jejunum and ileum and in the mesenteric lymph nodes, with concomitant infiltrates of mononuclear cells and giant cells; the latter were frequently found applied to the margins of the fatty deposits. There were no morphological changes in the pancreas and there was no evidence of active infection, tuberculous or other.

In the author's case a complete set of histochemical tests was performed with the purpose of ascertaining the nature of the fatty substances stored in the intestines and in the mesenteric lymph nodes. The results of these tests have been recorded with the description of the microscopical findings. Since the critical studies of Hueck (5) and of Kaufmann and Lehmann (6), it is evident that the fat stains employed do not possess the specificity formerly claimed for them. In the present instances, therefore, the results of staining merely support the supposition that the deposited material is a mixture of cholesterol, neutral fat, and fatty acids.

Concerning the significance and genesis of the lesions which have been described existing data justify negative statements only.

It is possible to exclude at once the hypothesis that the lipoid storage is merely a phase of normal alimentation and absorption. The

extensive investigations of Dabelow (7) on normal absorption of fat show changes not comparable qualitatively or quantitatively with those under consideration here. The more recent studies by Danby (8) lead to a similar view.

A more direct negation is provided by routine postmortem material, in which all phases of digestion and absorption are necessarily encountered and in which lipoid storage of the unusual type under discussion is not found.

The ingestion of unusual substances and their subsequent absorption and storage is not suggested by the case histories and is further rendered unlikely by the persistence of the steatorrhea during the prolonged hospitalization.

The differential anatomical diagnosis must consider sprue—to which the cases cited bear a strong clinical resemblance—and also diseases of lipoid storage. Congenital anomaly of lymphatics cannot be excluded.

With regard to sprue we are fortunate in possessing the thorough studies of T. E. Hess Thaysen (9). This author concludes that "it is very doubtful whether tropical sprue is associated with any characteristic anatomical changes in the intestines. Moreover, it seems that the morbid changes reported in some of the cases are so uncertain that one cannot attribute any real significance to them" (10). "In non-tropical sprue we meet with quite the same lack of characteristic changes in the intestinal mucosa as in the tropical form" (11).

Thaysen cites in detail the gross and microscopical findings of all cases available in the literature. These descriptions, which are accompanied by photomicrographs, uniformly fail to depict lesions resembling those which form the subject of the present discussion. A case of "pancreatogenous fatty diarrhoea" subjoined by Thaysen likewise shows no such lesions.

Differential diagnosis must finally consider cases of local and general lipoid storage. The former are represented by islands of lipoid deposit in the gastric and intestinal mucosa—the Lipoid-Inseln of Lubarsch and Borchardt (12) and the Lipoid-Zellenknötchen of Feyrter (13). These lesions which are described as consisting of clumps of cells containing fat droplets, are small and sharply localized, and are not associated with giant cells. The lipoid is present in

minute masses a few micra in size. Moreover, the lesions are not known to be associated with symptomatic disturbances. Finally, their occurrence is limited to middle-aged or old people. All of these characteristics indicate that lesions of this type have nothing to do with the widespread lesions at present under consideration.

The generalized lipoidoses—Gaucher's disease, Hand-Schüller-Christian's disease, and Niemann-Pick's disease—are excluded no less definitely by anatomical, chemical and clinical evidence. These diseases are characterized above all by widespread deposition of lipoids in the viscera, including the bones. The lipoids are found in a state of subdivision, in "foam cells"; in Gaucher's disease large turbid lipophages are seen. These appearances contrast sharply with the massive fatty agglomerations lying extracellularly in the tissues in the author's case. Foam cells, moreover, are often grouped in "cell nests" and, except in Gaucher's disease, are rarely giant cells. Gaucher's disease is further distinguished by the fact that its special lipoid (kerasin) is not stained by ordinary methods. The cases which have been detailed in the present discussion showed lipoid deposits limited to the intestines and the mesenteric nodes; the lipoid was shown to occur in large masses as well as in droplets, and was situated outside of cells, as well as intracellularly.

Thus it is evident that the three cases under discussion present lesions distinctly different from anything previously described and do not fall into existing categories. The author's case especially does not appear to belong in the category of lipoidosis. Dilatation of lymphatic vessels—obstructive or congenital—would seem to be the essential characteristic.

It will be noted that in addition to intestinal and lymphadenoid lesions which characterize all three cases in the series an additional group of lesions was found in two of the three—*i.e.* in Whipple's case and in the author's case. Each of these two patients had had arthritis (the joints were not examined postmortem) and both had extensive pericardial and pleural adhesions. Whipple's patient had organizing peritonitis and also cardiac hypertrophy and aortic endocarditis (verrucous). The author's patient had rheumatic verrucae on the mitral and tricuspid valves and Aschoff bodies in the myocardium.

Since the entire series of cases is so small it would be unwise to

venture an opinion with regard to a possible relation between the intestinal and the extra-intestinal lesions. In this matter judgment may well wait.

SUMMARY

An account is given of three autopsied cases of steatorrhea in young adults. All three were found to have unusual widespread deposits of lipoid material in large aggregations throughout the submucosa of the small intestine and in the mesenteric lymph nodes. Two of the patients in addition had chronic arthritis, rheumatic lesions of the heart, and extensive pericardial and pleural adhesions.

The intestinal lesions are shown to differ from those of any known morbid entity.

The cause and genesis of the lesions remain unexplained.

The author takes pleasure in acknowledging assistance given by Dr. Rich in the preparation of the present report.

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Note: The historical antiquarian will be interested in the essay by John Elliotson in the eighteenth volume of the Medico-Chirurgical Transactions, 1833, page 67, "On the Discharge of Fatty Matters from the Alimentary Canal and

Urinary Passages." Elliotson collected 17 cases, one of which came from Moellenbroccus (1671), another from Fabricius Hildanus (1746). The series is weird and heterogeneous and even includes cases of excretion of soaps after ingestion of olive oil.

PLATE 1

(Photographs by Mr. Milton Kougl)

FIG. 1. Jejunum (Whipple's case). Note blunt villi and greatly dilated lymphatics. These lymphatics were shown to be distended with fat. Haematoxylin-eosin stain. × 90.

FIG. 2. Jejunum (author's case). Note blunt villi and distended lymphatics. The latter were filled with fat. Haematoxylin-eosin stain. × 90.

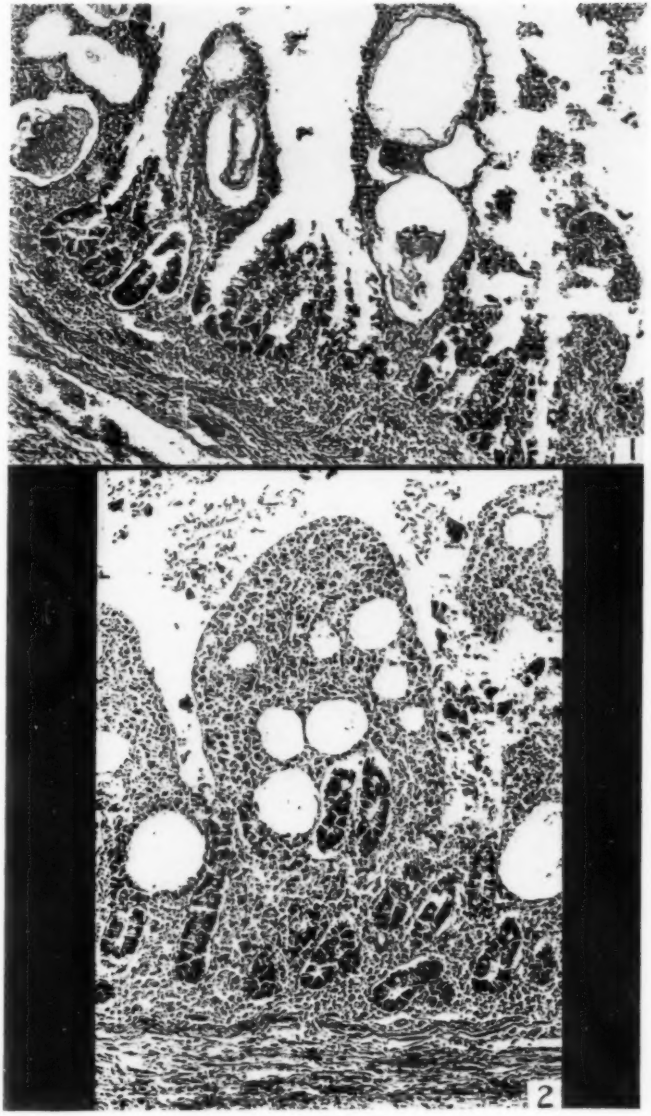
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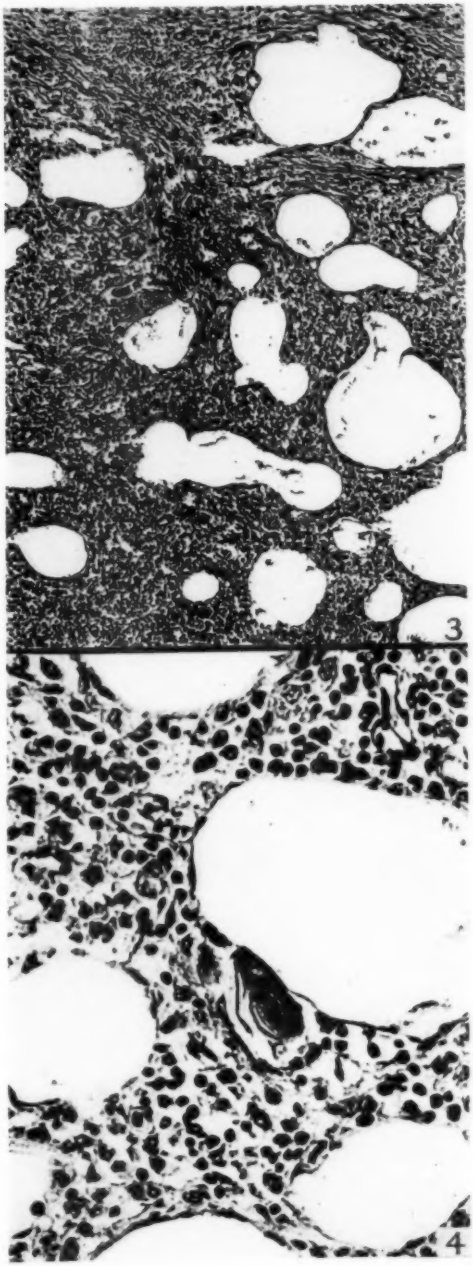
PLATE 2

(Photographs by Mr. Milton Kougl)

FIG. 3. Mesenteric lymph node (author's case). Note the distended sinuses, which were filled with fat. Haematoxylin-eosin stain. × 90.

FIG. 4. Mesenteric lymph node (author's case). Note multinuclear giant cell closely applied to the margin of a distended sinus. Haematoxylin-eosin stain. × 390.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A NOTE UPON THE ASSOCIATION OF HYPERTHYROIDISM AND PERNICIOUS ANAEMIA

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The association of hyperthyroidism and pernicious anaemia, though apparently uncommon, has been reported (Neusser (1), Hansen (2), Giffin and Bowler (3), Hanssen and Stub (4), Burwell (5), Reinhold (6), Meulengracht (7), J. G. Wilkinson (8), Fleischhans (9)). In 18 of the 23 cases described by these authors, pernicious anaemia developed in patients who had previously suffered from hyperthyroidism. In two instances (6, 8) both diseases were manifest at the time of the first observation of the patient. In the remaining three cases (8, 9) hyperthyroidism developed subsequently to the diagnosis of pernicious anaemia.

The association of these two diseases may be entirely fortuitous. However, their occurrence in three patients recently observed in the Johns Hopkins Hospital has provoked inquiry concerning the factors possibly common to both conditions.

Achlorhydria is nearly four times as common in patients with Graves' disease as in normal individuals. In earlier reports on the subject, as indicated recently by Bloomfield and Polland (10), the tests of gastric secretion were inadequate, and no consideration was given in the discussion of incidence to the occurrence of achlorhydria in normal individuals. Recently Lerman and Means (11), using the combined alcohol and histamine test, have found anacidity in 19 of 50 cases of hyperthyroidism, an incidence of 38 per cent, which when corrected for age becomes 45.6 per cent as compared with 12.6 per cent in normal individuals. The actual proportion of cases with anacidity in all of the studies reviewed by Bloomfield and Polland (10) and in Wilkinson's more recent report (12) (a total of 244 cases) is also 46 per cent.

The cause of such anacidity is unknown. In contrast with the permanent achlorhydria characteristic of pernicious anaemia, that associated with hyperthyroidism does not always persist. Berryhill and Williams (13) have reported recently that in 73 per cent of 26 patients with Graves' disease in whom achlorhydria was found before operation, the gastric acidity returned to a normal level after partial thyroidectomy. This would suggest that the disease of the thyroid, or the underlying disorder, in some way influences and impairs gastric secretion in a certain proportion of cases. It is possible, as suggested by Meulengracht (7), that achlorhydria, occurring as a result of hyperthyroidism, may predispose to the development of pernicious anaemia. It would seem important to test the gastric juice from patients with hyperthyroidism and achlorhydria for the presence of the blood-regenerating principle by its administration to patients with pernicious anaemia.

It has been shown that *hepatic damage* occurs in many cases of hyperthyroidism (14, 15) and it has recently been demonstrated that macrocytic anaemia may occur in association with disease of the liver (16, 17). However, it appears unlikely that the macrocytic anaemia observed in patients who have had Graves' disease is the result of liver damage. In contrast with the macrocytic anaemia of liver disease, that which has been observed following hyperthyroidism assumes the typical clinical picture of pernicious anaemia including glossitis, achlorhydria gastrica, and neurological changes.

If either achlorhydria or liver damage is of importance in the association of hyperthyroidism and pernicious anaemia, these factors would predispose to the latter; pernicious anaemia would follow hyperthyroidism. This is also the sequence which would be expected in view of the usual age incidence of these diseases. It is noteworthy that this has been the order of events in the great majority of instances heretofore recorded.

However, among the cases in the records of the Johns Hopkins Hospital, which constitute the basis of this report, this has not been the usual sequence. In one patient (S. W.), although goiter had been found nine years previously, symptoms of hyperthyroidism appeared at the same time as those of pernicious anaemia. In another, (J. P. B.) hyperthyroidism seemed to develop with the reappearance of

symptoms of Addisonian anaemia. In two more cases (H. D. & E. J. D.) the classical signs of hyperthyroidism became evident during remissions from pernicious anaemia induced by liver therapy. In the fifth case (E. J.) hyperthyroidism recurred following the appearance of pernicious anaemia and its treatment with liver.

Between the years 1910 and 1926 (June) there were 676 cases of hyperthyroidism and 335 cases of pernicious anaemia among a total of 30,208 admissions. The association of the two diseases was noted in two instances. Between July 1926, when liver therapy was instituted, and July 1, 1935, there were 504 cases of hyperthyroidism and 95 cases of pernicious anaemia out of a total of 19,535 admissions.

TABLE I

	1910–1926 (JUNE)	1926 (JULY)–1935 (JUNE)
	per cent	*per cent*
Incidence of pernicious anaemia in patients without hyperthyroidism	1.1 ± 0.03	0.5 ± 0.03
Incidence of pernicious anaemia in patients with hyperthyroidism	0.3 ± 0.1	0.6 ± 0.2
Difference	0.8 ± 0.1	0.1 ± 0.2
Incidence of hyperthyroidism in patients without pernicious anaemia	2.3 ± 0.6	2.6 ± 0.1
Incidence of hyperthyroidism in patients with pernicious anaemia	0.6 ± 0.3	3.2 ± 1.2
Difference	1.7 ± 0.7	0.6 ± 1.2

The two diseases were associated in three instances. The statistical data derived from this record of admissions are presented in table I. They suggest that among the patients admitted to this hospital the incidence of hyperthyroidism among cases of pernicious anaemia has increased in the period since 1926 as compared with the preceding sixteen years. It is to be noted, however, that prior to July 1926, pernicious anaemia occurred in association with hyperthyroidism less frequently than in patients without hyperthyroidism: likewise hyperthyroidism developed less often in cases of pernicious anaemia than in non-anaemic patients. Since the introduction of liver therapy the association of these two diseases has become equal to the incidence among the individuals without one of them. This is probably to be

explained by the development of more accurate diagnostic methods for each disease and by the longer life expectancy resulting from improved methods of treatment. There remains the possibility that the newer methods of treatment of pernicious anaemia may have influenced the development of hyperthyroidism in these cases.

Among the total of 22 cases (including our own) concerning which adequate information is available regarding treatment, of the six in which hyperthyroidism followed pernicious anaemia [Wilkinson (8) & Fleischhans (9) and our patients E. J., E. J. D., & H. D.] five had been treated with liver or hog's stomach; all of these patients were in remission as regards anaemia when the symptoms of Graves' disease were observed. Of the fourteen in which pernicious anaemia followed hyperthyroidism only two had received liver (7). In the remaining two instances (J. P. B. & S. W.) the two diseases appeared to develop simultaneously.

A study of the literature has yielded only two sorts of experimental observations which might bear upon the relation of the administration of liver to the development of hyperthyroidism. Hunt (18) has shown that the toxicity of acetonitrile for mice is closely related to the activity of the thyroid; minute amounts of the desiccated gland fed to these animals bring about a pronounced increase in their resistance to acetonitrile. In the course of an investigation of the effects of diet upon the resistance to acetonitrile, Hunt (19) found that, among a large variety of foods, liver produced the greatest increase in resistance to acetonitrile, and that the resistance so induced was diminished by half following thyroidectomy (20). Marine (21, 22) has reported that "a diet of liver, particularly pig's liver, produces distinct hypertrophy of the thyroid glands of rats, with reduction in the amount of colloid and increase in size of the thyroid cells. Such food also leads to hyperplasia of the thyroid of brook trout."

To be sure, these experimental results deal with apparent functional or histological alterations in the thyroid gland. Their significance with regard to the pathogenesis of Graves' disease remains to be demonstrated. The present writers have been unsuccessful in an attempt to produce hyperthyroidism in rats by the injection of liver extract or even by feeding raw liver. In their opinion the association of hyperthyroidism and pernicious anaemia in patients in this

hospital has been simply fortuitous. These cases are recorded in the hope of stimulating confirmatory or contradictory reports from other clinics.

SUMMARY

1. Five cases are described in which hyperthyroidism and pernicious anaemia developed in the same patient.

2. A total of 23 such cases has been previously reported.

3. The significance of the association of these two diseases is discussed in regard to:

(a) The achlorhydria which is frequently encountered in cases of Graves' disease.

(b) The hepatic damage which may occur in hyperthyroidism.

(c) The greater expectancy of life for each disease afforded by the newer methods of treatment.

(d) The possible thyrogenic influence of liver.

Case I. J. P. B. Med. No. 28050. White male, aged 54 years. Pernicious anaemia; hyperthyroidism 17 months later with moderate relapse of pernicious anaemia.

This patient was admitted to the Johns Hopkins Hospital in November 1910, complaining of loss of weight and weakness gradually increasing over the preceding two years. Prior to that time his health had been good. For six months he had noticed tingling and numbness in the toes and fingers. His appetite had diminished.

The patient was emaciated, the skin pale with a gray tinge. The mucous membranes were pale, the tongue red and swollen. There was no free hydrochloric acid in the gastric contents after an Ewald meal. Blood examination showed R.B.C. 3,300,000; Hb. 105%; W.B.C. 3,600.

During 39 days in the hospital the patient gained 17 pounds and was discharged improved. The R.B.C. had risen to 4,296,000; Hb. 100%. At another hospital, several months later, the blood examination revealed: R.B.C. 5,140,000; Hb. 99%. Exploratory laparotomy was performed and no abnormality discovered.

October 15, 1911. The patient returned to the Johns Hopkins Hospital complaining of loss of weight, and of numbness and tingling in the legs.

Examination showed undernutrition, slight jaundice of sclerae, exophthalmos and lid-lag. The right lobe of the thyroid was enlarged; there was demonstrable dullness beneath the upper sternum. R.B.C. 2,820,000; Hb. 62%. Pulse varied between 90 and 120 per minute. The patient remained in the hospital until December 11, 1911. He received an abundant diet, Fowler's solution in doses

from 3 to 7 drops t.i.d., and dilute hydrochloric acid. Upon this regime he gained ten pounds in weight; the glossitis and stomatitis abated; and the blood count rose to: R.B.C. 4,600,000; Hb. 94%. The pulse rate persisted at about 100 per minute.

Case II. S. W. Unit 2336. White female, aged 61. Goiter; pernicious anaemia nine years later with hyperthyroidism.

The patient was admitted in January 1926 complaining of nervousness, weakness and swelling of the legs. The family history was of no interest. She had been in poor health for 20 years. Nine years previously she had been told that she had goiter. For five months before admission she had been troubled with pain in the bladder and difficulty in voiding. Nervousness and exhaustibility had increased during this time and the lump in her neck had become larger.

She was found to be undernourished and sallow, but not particularly nervous. The eyes were not prominent. Papillary atrophy of the tongue was noted. There was a fine tremor of the outstretched fingers. In the midline of the neck a cystic glandular mass, 3 cm. in diameter, was demonstrable.

The lateral lobes of the thyroid were quite firm. The cervical vessels pulsated vigorously; there was a loud bruit over the gland. The pulse was 140 and regular. B.P. 170/60. There was a loud systolic murmur over the whole precordium. Neurological examination negative. R.B.C.: 2,470,000; Hb. 60%; and in the smear there were many macrocytes, marked poikilocytosis and two normoblasts. W.B.C. 3,980. The Ewald meal showed no free acid. B.M.R. was +40, +41, +60 and continued high despite Lugol's solution. After a blood transfusion, the R.B.C. was 3,440,000; Hb. 59%. On March 15, 1926, double partial lobectomy was performed. Pathological examination of the tumor revealed multiple adenomata of the thyroid with degeneration, cyst formation and slight epithelial hyperplasia.

Following operation there was a steady rise of pulse and temperature for several days. The patient was greatly troubled with incontinence of urine. Cultures revealed staphylococci in large numbers. R.B.C., 2,750,000; Hb. 49%; W.B.C., 4,800. Her general condition soon became critical, the temperature and pulse rose and death occurred 20 days after operation. *Final diagnosis. Infected decubitus ulcers; staphylococcus septicaemia; abscesses of the heart, lungs, kidneys, and liver, acute splenic tumor with fresh infarct. Hyperplastic bone marrow; cystitis cystica.*

Case III. E. J. Unit 58140. White female, aged 43. Tabes dorsalis, hyperthyroidism three years later. Pernicious anaemia four years later with symptoms suggesting hyperthyroidism; after two years, return of latter symptoms, leading to second thyroidectomy; definite relapse of pernicious anaemia eight months later.

This patient first came to the Johns Hopkins Hospital in May 1924 complaining of unsteadiness of the knees. She had had measles in childhood but otherwise

had been very well until 1920 when "weakness" commenced. She had married twice and during the first marriage (1907) had given birth to three normal children. During the second marriage (1920) there were three pregnancies, all of which resulted in miscarriages at three and a half, four, and four and a half months, respectively. In 1923 the patient noticed weakness in the legs and unsteadiness of gait, and four months before admission a feeling of "walking on cushions" and inability to walk in the dark. Incontinence of urine, and morning diarrhoea had been present for three months.

Examination revealed unequal pupils which did not react to light, tabetic gait, positive Romberg, impairment of sensation in both legs, absence of all deep reflexes, vibratory sense lost in lower extremities. The mucous membranes were of normal color. Blood Wassermann consistently negative but spinal-fluid Wassermann positive (0.6 to 1.0 cc.). Globulin was four plus and the mastic curve 5,555,543,210. A diagnosis of tabes dorsalis was made and treatment with tryparsamide instituted. This was continued quite regularly for 17 months, at the end of which time considerable improvement was noted.

In March 1927, the patient was admitted to the Union Memorial Hospital complaining of nervousness, a lump in the neck and loss of weight. She had been nervous and weak for the past two years and had lost weight in spite of a good appetite. Recently she had noticed protrusion of the eyes and difficulty in swallowing.

Examination showed undernutrition, striking bilateral exophthalmos and lid-lag. There was a symmetrical enlargement of the thyroid with marked pulsation and a distinct bruit. The pulse was regular but rapid. B.P. 110/64. B.M.R. +31. A partial thyroidectomy was performed April 1927 (pathological diagnosis —exophthalmic goiter). Convalescence was uneventful.

The patient was readmitted to the Union Memorial Hospital in April 1932. She had enjoyed good health for four years, but in 1931 shortness of breath, tachycardia, loss of weight and nervousness returned. Three days prior to this admission she had suffered radiating "girdle-like" pains in the upper abdomen. The gait had become progressively more unsteady.

Physical examination: There was a yellowish pallor, marked exophthalmos, slight lid-lag, slight tremor of the extended hands and papillary atrophy of the tongue. The thyroid could not be felt. The pulse was 90. B.P. 120/72. The pupils were fixed; knee jerks, biceps and triceps reflexes absent; Romberg positive; the gait ataxic, B.M.R. +26, R.B.C. 1,790,000, Hb. 50%, W.B.C. 3,700. The blood smear showed many macrocytes. Gastric analysis (Ewald) failed to reveal free hydrochloric acid. The spinal-fluid Wassermann was positive, the blood Wassermann was negative. No globulin and only two lymphocytes were found in the spinal fluid. A diagnosis of pernicious anaemia was made. A high caloric Minot-Murphy diet and liver extract and iron were administered. The blood count rose rapidly and the patient's symptoms disappeared.

In May 1933 she was admitted to the Union Memorial Hospital for the third time. She had been feeling well since the last admission, but had taken liver

irregularly. Shortness of breath had returned but the gait had improved. R.B.C. 3,860,000; Hb. 75%. Spinal fluid normal.

The patient returned again in August of the same year complaining of increasing weakness, nervousness, and insomnia. Physical examination revealed exophthalmos, fixed pupils, absence of deep reflexes, pulse 90, B.P. 120/80. There was no definite tremor; the skin was warm but dry. No thyroid enlargement was demonstrable. B.M.R., +29, +14, +16. R.B.C. 4,120,000; Hb. 71%. With rest in bed the symptoms improved considerably.

In March 1934 she was readmitted to the Union Memorial Hospital because of extreme nervousness, severe dyspnoea, and weakness of the lower extremities. On this occasion the right lobe of the thyroid was found to be visibly and palpably enlarged; there was pronounced tremor of the fingers, pulse rate 88, B.P. 118/68, B.M.R. +34, +33. This fell to +15 in ten days, when the thyroidectomy was performed. Pathological diagnosis of the specimen was "hypertrophy and hyperplasia of the thyroid." The patient was discharged in good condition.

In August 1934, the patient returned to the Johns Hopkins Hospital complaining of weakness in the legs and difficulty in walking, which had developed about four months before. She complained of falling if she did not watch her feet, of numbness and tingling in the fingers during the past two months and of tightness across the abdomen. No new physical findings were noted excepting a systolic murmur heard over the base of the heart. The blood and spinal-fluid Wassermann were negative. In September B.M.R. was +25; R.B.C. 1,820,000; Hb. 6,8 gm. (47%); Mean Corpuscular Volume 121 cu. μ; W.B.C. 4,200. Examination revealed pallor, exophthalmos, Argyle-Robertson pupils, smooth tongue, enlargement of the thyroid, soft systolic cardiac murmur, pulse rate 96, palpable spleen, fine tremor of the hands, slight ataxia of the upper extremities, slight flaccidity of the lower extremities, gross ataxia in heel-knee test, loss of position sense, absent triceps, biceps, knee- and ankle-jerks and loss of vibratory sense in the lower extremities. Spinal fluid showed four plus Wassermann (0.6 to 1.0 cc.), 25 mgm. protein.

Intramuscular liver therapy (Lederle) was instituted at once, 3 cc. being given every other day in addition to 1200 cc. domestic liver extract daily. The B.M.R. six days after admission, and five days after starting treatment was +17. Nine days later it was +7. On this date, the reticulocyte peak of 14.5 per cent was reached. At the time of the patient's discharge the R.B.C. were 4,400,000; Hb. 11.5 gm. (79%) and Mean Corpuscular Volume 88 cu. μ. Neurological signs were precisely the same as on admission but the subjective tingling and girdle pains had disappeared.

Case IV. E. J. D. Unit 24724. White female, aged 31. Pernicious anaemia with moderately advanced cord degeneration; hyperthyroidism five years later.

This patient first appeared in May 1929 complaining of numbness and weakness of the hips and legs. Her mother had died in her 42nd year of "inflammation of

the kidney" and had been considered very anaemic. Her father died at 59 years of "Bright's disease." A brother had died at 40 years of tuberculosis. Until 1926 she had been quite well. Since 1916 she had been an acrobatic dancer. In 1918 a laparotomy had been performed and at that time the appendix and perhaps some pelvic organs had been removed.

In October 1926, during convalescence from pneumonia, she noticed numbness in her feet. "Anaemia" was discovered at this time. In the spring of 1928 she developed "septic poisoning" from a tooth and remained in bed for seven weeks. In November of the same year she was forced to bed with pleurisy. At this time it was noticed that the numbness in the feet had increased. By April 1929, the numbness seemed to creep upwards. The patient noticed difficulty in controlling the legs, unsteady gait, and weakness and stiffness in the arms and hands. The physical findings on admission (May 1929) have been fully reported elsewhere (Baker, Bordley and Longcope, case 3); it will suffice here to say that these indicated pernicious anaemia and subacute degeneration of the spinal cord. R.B.C. 2,390,000; Hb. 60%. Liver therapy was instituted and was followed by excellent blood response and considerable neurologic improvement.

It was noted on this admission that the patient was very unstable and emotional, wept often and tended to be very sullen; that the eyes were "normally prominent" and the thyroid not enlarged.

In May 1931, the patient returned complaining of double vision and protrusion of the eyes, of five months' duration. She had taken liver extract regularly since discharge. For a month prior to admission she had noted increased appetite, excitability, a sense of fullness in the neck, and loss of seven pounds in weight. The patient was strikingly overactive and nervous and showed pronounced exophthalmos. The pulse was 120; B.P. 130/70; and there was a fine tremor of the fingers, hands, and tongue. Both lobes and the isthmus of the thyroid gland were enlarged and firm. All the deep reflexes were exaggerated but equal; ankle clonus was sustained for only a few jerks on either side; the Babinski was positive on both sides, two-point discrimination was poor over the ankles, there was slight ataxia in the heel-knee test, and the vibratory sense was absent on both ankles. The blood showed 3,590,000 red corpuscles and 75 per cent Hb. The B.M.R. was +36, +36, +67 and +38. Double partial lobectomy was performed on June 17, 1931. The pathological diagnosis of the thyroid tissue removed was "exophthalmic goiter." Recovery was satisfactory and B.M.R. on discharge was 0. The status of the patient since this time has remained essentially unchanged. She is still somewhat irritable and unstable. The last blood count, June 1935, showed 5,360,000 red corpuscles and 15.0 gm. (103%) Hb

Case V. H. D. Unit 54434. White male, aged 47. Pernicious anaemia: hyperthyroidism six months later.

The patient first appeared in March 1934 complaining of swelling of the ankles, loss of taste, shortness of breath, and nycturia. Ten months previously he had

noticed some loss of weight; six months before urinary frequency had appeared with the sensation that the bladder could not be emptied. Increasing languor, weakness, and dyspnoea were first noted six weeks before admission. The tongue had become sore ten days before entry to the ward. Weakness, "wobbly" sensations in the legs, and pallor, forced the patient to come to the hospital.

On examination the following signs were noted: slight undernutrition and dyspnoea, marked yellowish pallor, slight cyanosis of the lips, irregular brownish pigmentation of the hands, right lenticular cataract, some papillary atrophy about the tip and edges of the tongue, slight enlargement of the heart, systolic murmurs at the apex, heart rate slow (70–80) rhythm regular, B.P. 140/180, distension of the urinary bladder, massive oedema of the legs, ankles, and feet, slight oedema of the sacrum, slight diminution of vibratory sense in the legs. The patient was despondent, apathetic and uncooperative. R.B.C. 2,040,000; Hb. 10.2 gm. (70%); Mean Corpuscular Volume 153, leucocyte count 3600, gastric analysis (histamine) revealed no free hydrochloric acid, the plasma proteins were 5.31 gm. per cent. Blood and spinal-fluid Wassermann negative.

Diagnosis: pernicious anaemia, arteriosclerosis, paralysis of the urinary bladder and hypoproteinaemia.

Liver therapy (liver extract, Lederle, 3 cc. intramuscularly and domestic liver extract, 1200 cc. orally) was initiated. Reticulocytes rose to a peak of seven per cent and on discharge R.B.C. were 3,710,000; Hb. 11.8 gm. (81%). The patient was subjectively improved. In December 1934 he returned to the dispensary with the complaint that during the past month dyspnoea had increased. He complained, too, of attacks of severe precordial pain. This occasionally radiated down the left arm, appeared on exertion, and was relieved by rest. Pulse 104. B.P. 130/60, R.B.C. 4,430,000; Hb. 14.2 gm. (98%). Mean Corpuscular Volume 100 c. μ. The heart rate was 70, the rhythm somewhat irregular. The administration of digitalis was followed by clinical improvement.

On January 5, 1935, the patient was readmitted to the hospital for observation. He complained of short attacks of pain in the epigastrium. The skin was warm and moist, the lobes of the thyroid were just palpable, a diastolic bruit was audible over them. There was no exophthalmos, and no evidence of myocardial insufficiency. Pulse 104 per minute, and regular. B.P. 140/66. There was a fine tremor of the extended hands. R.B.C. 3,880,000; Hb. 13.5 gm. (93%), Mean Corpuscular Volume 14 cu. μ, B.M.R. +22, +41, and +42 at five-day intervals.

During this period there occurred several attacks of tachycardia. The pulse rate suddenly increased to 144 per minute; this fell to 72 during pressure over the carotid artery in the neck. Electrocardiographic diagnosis: Auricular flutter with 1:1 response.

Following the administration of Lugol's solution the metabolic rate fell to +21. Double partial lobectomy was performed February 8, 1935. Pathological diagnosis of the specimen removed was: "goiter with slight epithelial hyperplasia and adenomata of the thyroid." Recovery from operation was uneventful and on

discharge B.M.R. was minus 2, pulse 75 and regular. The attacks of cardiac pain did not recur after the B.M.R. had fallen to normal.

Diagnosis: Pernicious anaemia, diffuse goiter with hyperthyroidism.

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BOOK REVIEWS

The Technique of Post Mortem Examination. By D. R. COMAN. 1st ed., 47 pp. illus. $1.40. (*Renouf Publishing Co., Montreal, 1934.*)

This small volume contains a clear and brief explanation of the manner in which autopsies are performed at the Royal Victoria Hospital, McGill University, Montreal; and there are a number of useful drawings to illustrate points of technique. A table of the weights of normal organs, and a description of frozen section technique for rapid microscopical examination of fresh tissues are also included.

S. B.

Examination of the Patient and Symptomatic Diagnosis. By JOHN WATTS MURRAY. Second Edition. 1219 pp. ill. $10.00. (*C. V. Mosby, St. Louis, 1936.*)

Dr. Murray, writing for the general practitioner, lays proper and needed stress on two requirements for a successful diagnosis: individualization of the patient and a thorough-going anamnesis. He offers what is essentially a check-list of innumerable and, for the most part, sensible questions to be asked of the patient during the taking of the history and to be posed by the doctor to himself during the physical examination. One-third of the volume considers symptoms by name and then by topography; the other two-thirds discusses symptoms of diseases by systems. Much pertinent material is listed, of the kind the physician should always have in the back of his head.

The method of presentation is the same antiphony of question and answering comment so rightly criticized by a recent reviewer in these columns as sacrificing "smoothness and literary tone to lucidity." The comments too often amount merely to long lists of diagnostic possibilities, though in Section II much space is given to differential diagnosis.

Readability and quick reference would be enhanced by variations in type size and face and by subject-group identification at the page-tops. The index is adequate and the 274 illustrations are well chosen.

N. B. C.

Physiology in Health and Disease. By CARL J. WIGGERS. 1156 pp. Illus. 1934. $9.00. (*Lea and Febiger, Philadelphia, Pa.*)

The author of this book felt the need of a text which, in addition to presenting physiology as a preclinical science, would attempt to correlate functions studied in the laboratory with the physiological disturbances produced by disease in patients. This worthy and ambitious goal is more difficult to attain in some divisions of the subject than in others and has been most successfully accomplished

by the author in his own field of cardiovascular function. The plan has led to the inclusion in a textbook of physiology of chapters with such headings as: *Polycythemia and Anemia; Clinical Disturbances of Respiration; The Dynamics of Valvular Lesions; Circulatory Failure; Edema; Urinary Secretion and its Perversions.* The presentation is detailed with liberal reference both to individual papers and to important monographs.

C. W.

Clinical Heart Disease. By SAMUEL A. LEVINE, M.D. 445 pp. 97 illustrations. Cloth $5.50. (*W. B. Saunders Co., Philadelphia and London.*)

This book is written especially for the general practitioner by a heart specialist whose wide experience in diseases of the cardiovascular system well qualifies him to present the useful facts of his subject. The various topics are developed in a very simple and understandable fashion with the aid of many pertinent illustrative cases drawn from the author's own experience. Especially good are the chapters on diseases of the pericardium and on the patient with heart disease as a surgical or obstetrical risk. No better consideration of the use of quinidine can be found. Occasionally reading becomes somewhat difficult, because many unimportant features are discussed in too much detail. Repetition has seemed advisable to the author in many places in order to prevent the reader from having to refer too often to one part of the book while reading another. For such a short treatise this has been done too often and in too careful detail.

The section on the treatment of congestive heart failure could have profitably been given in greater detail at the expense of less valuable material which was included.

On the whole the book should be of value to the medical student and general practitioner, although it is not a particularly outstanding contribution in a field which is already filled with many excellent treatises of a similar nature. No attempt is made to include any references.

A. M. H.

Pediatric Nursing. By JOHN ZAHORSKY and BERYL E. HAMILTON. 568 pp. $3.00. (*C. V. Mosby Co., St. Louis, 1936.*)

In this first edition, we find a rather complete, well-balanced, clearly presented treatment of the subject that should be of value to both student and instructor in Pediatric Nursing. The book in its entirety may be too comprehensive to be adequately covered as a text, yet by a selective process the discriminating instructor will find material sufficient to meet the demands of the various types of nursing classes.

The modern trends in Pediatric Nursing are duly considered. The normal child with his proper nutrition, physical and mental development must serve as a basis for the understanding of the ill patient. This book teaches the nursing care of the newborn in the home, the set-up of the nursery, the preparation of

foods, the technic of feeding, and of teaching the mother. The chapters on "The Sick Infant in the Home," "The Home and the Family," and "Child Psychology" are timely and to the point. Another modern trend is the prevention of disease. This is emphasized by calling attention to the meaning of infectious diseases, the sources of contagion, the modes of transmission, the prophylaxis of isolation and preventive nursing measures.

Part I is devoted to the Science of Pediatrics and forms the major portion of the book. General considerations and descriptions are given of various children's diseases.

Part II treats of the Practice of Pediatric Nursing and is taught by actual demonstration. The methods of procedure have apparently been selected from the technics used in various large hospitals of recognized standing.

The illustrations throughout are numerous especially in the part dealing with nursing procedures. The principles illustrated are good. In some, the antiquity of background detracts from the effectiveness of the picture.

On the whole, a most satisfactory book.

M. L. G.

Guide to Psychiatric Nursing. By F. A. CARMICHAEL and DR. JOHN CHAPMAN. 2nd ed., revised. 175 pp. illus. $2.25. (*Lea & Febiger, Philadelphia, 1936.*)

The first edition of this book was found unattractive in format and lacked illustrations, but this revised edition contains new thought and practice in psychiatry as well as descriptive illustrations, both pictorial and written, and will provide the nurse, who has not had training in psychiatry, with a book that will give her a working knowledge for the nursing of psychiatric patients.

The history and present status of psychiatry; definitions, classification, etiology, and symptomatology of mental diseases; organic reaction types and psychoses associated with somatic disease; mental deficiency and epilepsy; psychoneuroses; functional psychoses; all are dealt with, and the ethics and duties of the psychiatric nurse are discussed clearly and concisely. The two appendices discuss hereditary factors in mental defect and disease, and the proposed modification of the present classification of mental diseases.

This book answers its purpose in an excellent manner. Its outline of mental diseases is easily understood; the chapters on symptomatology and nursing duties are particularly good; special treatments are described in detail. Although written mainly for the beginner in psychiatric nursing in a state institution, the book can be used to advantage as a supplementary text for students and as a guidebook for nurses who are trained in psychiatry, to freshen their memories in this field.

A. K.

Passive Vascular Exercises. By LOUIS G. HERRMANN. 288 pp. Illus. $4.00. (*J. B. Lippincott Co., Philadelphia, 1936.*)

This monograph is an exposition of the method of treatment developed by the author and his associates in Cincinnati and a description of their experiences

with it, in their revival of the conception that changes in environmental air pressure may affect favorably the peripheral arterial circulation. As a subtitle indicates, there is also much in the book concerning the conservative management of obliterative arterial disease of the extremities.

A long chapter is devoted to the historical development of the subject, the use of negative pressures being referred back to Nathan Smith in 1798 and the use of alternate applications of suction and pressure to Edgar Bluck in 1887.

There follow chapters on the physiology of the peripheral distribution of blood, the collateral arterial circulation in human extremities, the general management of peripheral vascular diseases, the passive vascular exercise method of therapy, clinical experiences with this method including the results obtained, indications for its use and contraindications. A final chapter presents a routine for the study and care of patients with organic arterial diseases.

Although the author in formal statements is careful to avoid exaggerated claims, nevertheless a note of propaganda creeps into many sections of the work, as is only natural when the writer is himself thoroughly convinced of the value of the method described.

The plan of therapy has excited wide spread interest and has attracted quite a following. There are, too, quite a few determined critics among surgeons of large experience with peripheral vascular diseases. Some of these wave it away with the statement that the idea is periodically revived and never gets anywhere and that the results claimed for it merely illustrate cases that are following the natural course of the disease. Others have had unfortunate results in early attempts to apply the method and are therefore prejudiced against it. Certainly the current revival of the idea has excited much more interest than ever before. This may be due to a variety of factors, for example: (1) a firmer foundation has been established for it in the physiological studies by Landis as well as by the Cincinnati group; (2) there is a more general knowledge of peripheral vascular diseases; (3) there is a greater interest among surgeons in conservative methods of treating these diseases; (4) there is a revival of interest in physical therapeutic procedures in general; and (5) efficient and convenient sets of apparatus have been developed and placed on the market by at least five different manufacturers who are actively engaged in bringing them to the attention of the medical profession.

The book may not convert confirmed antagonists of the method, but it will be very welcome to those who are trying to give it a fair and thorough trial.

T. P. S.